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| (30) Priority Data: 233,166 26 April 1994 (26.04.94) US 404,565 21 March 1995 (21.03.95) US 404,566 21 March 1995 (21.03.95) US | | (74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US). | |
| (60) Parent Applications or Grants (63) Related by Continuation US 404,565 (CIP) Filed on 21 March 1995 (21.03.95) US 404,566 (CIP) Filed on 21 March 1995 (21.03.95) US 233,166 (CIP) Filed on 26 April 1994 (26.04.94) | | (81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). | |
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| (54) Title: SUBSTITUTED SULFONAMIDES AS SELECTIVE β_3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY | | | |
| <p style="text-align: right;">(I)</p> | | | |
| <p>(57) Abstract</p> <p>Substituted sulfonamides having formula (I), are selective β_3 adrenergic receptor agonists with very little β_1 and β_2 adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduce neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for increasing gut motility are also disclosed.</p> | | | |

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- 1 -

TITLE OF THE INVENTION

SUBSTITUTED SULFONAMIDES AS SELECTIVE β_3 AGONISTS
FOR THE TREATMENT OF DIABETES AND OBESITY

5 CROSS REFERENCE

This is a continuation-in-part of co-pending application U.S.S.N. 08/233,166 filed April 26, 1994, which is hereby incorporated by reference in its entirety.

10 BACKGROUND OF THE INVENTION

β -Adrenoceptors have been subclassified as β_1 and β_2 since 1967. Increased heart rate is the primary consequence of β_1 -receptor stimulation, while bronchodilation and smooth muscle relaxation typically result from β_2 stimulation. Adipocyte lipolysis was initially thought to be solely a β_1 -mediated process. However, more recent results indicate that the receptor-mediating lipolysis is atypical in nature. These atypical receptors, later called β_3 -adrenoceptors, are found on the cell surface of both white and brown adipocytes where their stimulation promotes both lipolysis (breakdown of fat) and energy expenditure.

20 Early developments in this area produced compounds with greater agonist activity for the stimulation of lipolysis (β_3 activity) than for stimulation of atrial rate (β_1) and tracheal relaxation (β_2). These early developments disclosed in Ainsworth *et al.*, U.S. Patents 4,478,849 and 4,396,627, were derivatives of phenylethanolamines.

25 Such selectivity for β_3 -adrenoceptors could make compounds of this type potentially useful as antiobesity agents. In addition, these compounds have been reported to show antihyperglycemic effects in animal models of non-insulin-dependent diabetes mellitus.

30 A major drawback in treatment of chronic diseases with β_3 agonists is the potential for stimulation of other β -receptors and subsequent side effects. The most likely of these include muscle tremor (β_2) and increased heart rate (β_1). Although these phenylethanolamine

- 2 -

derivatives do possess some β_3 selectivity, side effects of this type have been observed in human volunteers. It is reasonable to expect that these side effects resulted from partial β_1 and/or β_2 agonism.

More recent developments in this area are disclosed in
5 Ainsworth *et al.*, U.S. Patent 5,153,210, Caulkett *et al.*, U.S. Patent
4,999,377, Alig *et al.*, U.S. Patent 5,017,619, Lecount *et al.*, European
Patent 427480 and Bloom *et al.*, European Patent 455006.

Even though these more recent developments purport to
10 describe compounds with greater β_3 selectivity over the β_1 and β_2
activities, this selectivity was determined using rodents, in particular,
rats as the test animal. Because even the most highly selective
compounds, as determined by these assays, still show signs of side
effects due to residual β_1 and β_2 agonist activity when the compounds
are tested in humans, it has become apparent that the rodent is not a
15 good model for predicting human β_3 selectivity.

Recently, assays have been developed which more
accurately predict the effects that can be expected in humans. These
assays utilize cloned human β_3 receptors which have been expressed in
Chinese hamster ovary cells. See Emorine *et al.*, Science, 1989,
20 245:1118-1121; and Liggett, Mol. Pharmacol., 1992, 42:634-637. The
agonist and antagonist effects of the various compounds on the
cultivated cells provide an indication of the antiobesity and antidiabetic
effects of the compounds in humans.

25 **SUMMARY OF THE INVENTION**

The instant invention is concerned with substituted
sulfonamides which are useful as antiobesity and antidiabetic
compounds. Thus, it is an object of this invention to describe such
compounds. It is a further object to describe the specific preferred
30 stereoisomers of the substituted sulfonamides. A still further object is
to describe processes for the preparation of such compounds. Another
object is to describe methods and compositions which use the
compounds as the active ingredient thereof. Further objects will
become apparent from reading the following description.

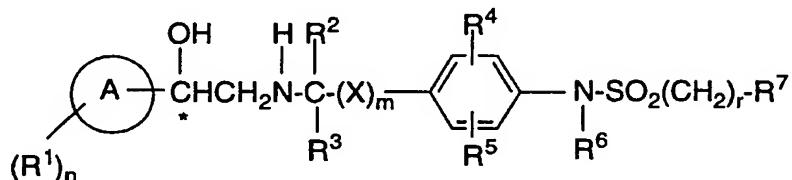
- 3 -

DESCRIPTION OF THE INVENTION

The present invention provides compounds having the formula I:

5

10



I

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where

n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

20

A is (1) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, (2) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,

25

(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,

(4) phenyl, or

30

R1 is (5) a benzene ring fused to a C₃-C₈ cycloalkyl ring;

(1) hydroxy,

(2) oxo,

(3) halogen,

(4) cyano,

(5) NR₈R₈,

- 4 -

- (6) SR⁸,
(7) trifluoromethyl,
(8) C₁-C₁₀ alkyl,
5 (9) OR⁸,
(10) SO₂R⁹,
(11) OCOR⁹,
(12) NR⁸COR⁹,
(13) COR⁹,
10 (14) NR⁸SO₂R⁹,
(15) NR⁸CO₂R⁸, or
(16) C₁-C₁₀ alkyl substituted by hydroxy, halogen, cyano,
NR⁸R⁸, SR⁸, trifluoromethyl, OR⁸, C₃-C₈ cycloalkyl,
phenyl, NR⁸COR⁹, COR⁹, SO₂R⁹, OCOR⁹, NR⁸SO₂R⁹ or
NR⁸CO₂R⁸;
- 15 R² and R³ are independently
(1) hydrogen,
(2) C₁-C₁₀ alkyl or
(3) C₁-C₁₀ alkyl with 1 to 4 substituents selected from
hydroxy, C₁-C₁₀ alkoxy, and halogen;
- 20 X is (1) -CH₂-,
(2) -CH₂-CH₂- ,
(3) -CH=CH- or
(4) -CH₂O-;
- 25 R⁴ and R⁵ are independently
(1)hydrogen,
(2) C₁-C₁₀ alkyl,
(3) halogen,
(4) NHR⁸,
(5) OR⁸,
30 (6) SO₂R⁹ or
(7) NHSO₂R⁹;
- R⁶ is (1) hydrogen or
(2) C₁-C₁₀ alkyl;
- R⁷ is Z-(R^{1a})_n;

- 5 -

- R^{1a} is (1) R¹, with the proviso that when A is phenyl, R^{1a} is not C₁-C₁₀ alkyl,
5 (2) C₃-C₈ cycloalkyl,
(3) phenyl optionally substituted with up to 4 groups independently selected from R⁸, NR⁸R⁸, OR⁸, SR⁸ and halogen, or
(4) 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, R⁸, NR⁸R⁸, OR⁸, SR⁸, and halogen;
- 10 Z is (1) phenyl,
(2) naphthyl,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(4) a benzene ring fused to a C₃-C₈ cycloalkyl ring,
(5) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
(6) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or
20 (7) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C₃-C₈ cycloalkyl ring;
- 25 R⁸ is (1) hydrogen,
(2) C₁-C₁₀ alkyl,
(3) C₃-C₈ cycloalkyl,
(4) Z optionally having 1 to 4 substituents selected from halogen, nitro, oxo, NR¹⁰R¹⁰, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkylthio, and C₁-C₁₀ alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO₂H, CO₂-C₁-C₁₀ alkyl, SO₂-C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₁-

- 6 -

C₁₀ alkoxy, and Z optionally substituted by from 1 to 3 of halogen, C₁-C₁₀ alkyl or C₁-C₁₀ alkoxy, or
5 (5) C₁-C₁₀ alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO₂H, CO₂-C₁-C₁₀ alkyl, SO₂-C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkyl, and Z optionally substituted by from 1 to 4 of halogen, C₁-C₁₀ alkyl or C₁-C₁₀ alkoxy;

R⁹ is (1) R⁸ or

(2) NR⁸R⁸;

10 R¹⁰ is (1) C₁-C₁₀ alkyl, or

(2) two R¹⁰ groups together with the N to which they are attached formed a 5 or 6-membered ring optionally substituted with C₁-C₁₀ alkyl; or

a pharmaceutically acceptable salt thereof.

15 In one embodiment of the instant invention A is a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or a 5 or 6-membered heterocyclic ring with from 20 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen.

In another embodiment of the instant invention A is phenyl or benzene fused to a C₃-C₈ cycloalkyl ring.

25 Preferred compounds of the instant invention are realized when in the above structural formula I:

R² and R³ are hydrogen or methyl;

X is -CH₂-;

n is 0 to 3;

30 m is 1;

r is 0 to 2; and

R⁴, R⁵ and R⁶ are hydrogen.

Other preferred compounds of the instant invention are realized when in the above structural formula I:

- 7 -

A is phenyl or a 6-membered heterocyclic ring with 1 or 2 heteroatoms selected from nitrogen and sulfur;

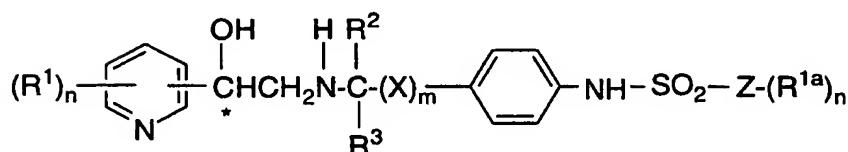
R¹ is hydroxy, halogen, cyano, trifluoromethyl, NR⁸R⁸, NR⁸SO₂R⁹, NR⁸COR⁹, NR⁸CO₂R⁸, C₁-C₆ alkyl
5 optionally substituted by hydroxy; and

r is 0 or 2.

More preferred compounds are represented by the formula

Ia:

10



15

Ia

wherein

n is 0 to 3;

m is 1

20 R¹ is (1) halogen or
(2) NR⁸R⁸;

R², R³ are independently hydrogen or methyl;

R^{1a} is (1) halogen,
(2) C₁-C₁₀ alkyl,

25 (3) NR⁸R⁸,
(4) NR⁸COR⁹,
(5) NR⁸CO₂R⁸,
(6) COR⁹,

30 (7) OCOR⁹, or
(8) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, halogen, R⁸, NR⁸R⁸, OR⁸, and SR⁸;

Z is (1) phenyl,
(2) naphthyl,

- 8 -

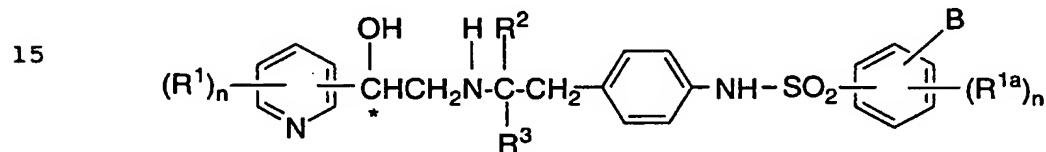
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
 5 (4) benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, or

(5) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C₃-C₈ cycloalkyl ring;

X is -CH₂-; and

10 R⁸ and R⁹ are as defined under formula I.

Even more preferred compounds are those represented by formula Id:



20 n is 0 or 1;
 R¹ is NR⁸R⁸;

R² and R³ are independently
 (1) hydrogen, or

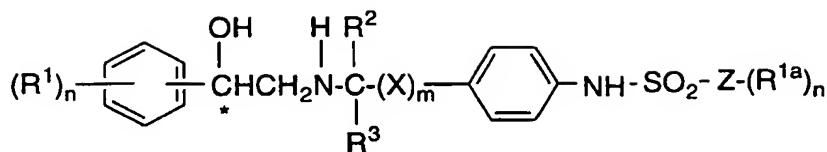
25 (2) methyl;
 B is (1) hydrogen,
 (2) benzene fused to the benzene ring to form naphthyl, or
 (3) a 5 or 6-membered heterocycle with 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen atom fused to the benzene ring;

30 R^{1a} is (1) halogen,
 (2) C₁-C₁₀ alkyl,
 (3) NR⁸R⁸,
 (4) NR⁸COR⁹,
 (5) NR⁸CO₂R⁸,

- 9 -

- (6) COR⁹, or
(7) a 5 or 6-membered heterocycle with from 1 to 4
heteroatoms selected from oxygen, sulfur and nitrogen,
optionally substituted with up to four groups independently
selected from oxo, R⁸, SR⁸, OR⁸, and NR⁸R⁸;
when B and the benzene ring form a fused ring system, R^{1a}
is attached to either ring;
- 5 R⁸ is
 (1) hydrogen,
 (2) C₁-C₁₀ alkyl,
 (3) Z optionally having 1 to 4 substituents selected from
 nitro, oxo, and NR¹⁰R¹⁰, or
 (5) C₁-C₁₀ alkyl having 1 to 4 substituents selected from
 hydroxy, halogen, C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, and Z
 optionally substituted by from 1 to 4 of halogen, C₁-C₁₀
 alkyl or C₁-C₁₀ alkoxy;
- 10 R⁹ is
 (1) R⁸ or
 (2) NR⁸R⁸;
- 15 R¹⁰ is
 (1) C₁-C₁₀ alkyl, or
 (2) two R¹⁰ groups together with the N to which they are
 attached formed a 5 or 6-membered ring optionally
 substituted with C₁-C₁₀ alkyl; and
- 20 Z is
 (1) phenyl,
 (2) a 5 or 6-membered heterocyclic ring with from 1 to 4
 heteroatoms selected from oxygen, sulfur and nitrogen,
 (3) a benzene ring fused to a 5 or 6-membered heterocyclic
 ring with from 1 to 4 heteroatoms selected from oxygen,
 sulfur and nitrogen, or
 (4) a 5 or 6-membered heterocyclic ring with from 1 to 4
 heteroatoms selected from oxygen, sulfur and nitrogen
 fused to a C₃-C₈ cycloalkyl ring.
- 25 Other more preferred compounds are represented by
 formula Ib:
- 30

- 10 -



5

Ib

wherein

- 10 n is 0 to 3;
- m is 1
- R¹ is
 - (1) hydroxy,
 - (2) cyano,
 - (3) NR⁸R⁸ or
 - (4) halogen;
- 15 R^{1a} is
 - (1) halogen,
 - (2) NR⁸R⁸,
 - (3) NR⁸COR⁹,
 - (4) NR⁸CO₂R⁸,
 - (5) OCOR⁹, or
 - (6) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, halogen, R⁸, NR⁸R⁸, OR⁸ and SR⁸;
- 20 Z is
 - (1) phenyl,
 - (2) naphthyl or
 - (3) benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen;
- 25 X is -CH₂-; and
- 30 R² and R³ are independently hydrogen or methyl.

Representative antiobesity and antidiabetic compounds of the present invention include the following:

N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

- 11 -

- N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide
- 5 N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide
- 10 N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-5-benzisoxazolesulfonamide
- N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide
- 15 N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(dimethylaminocarbonyl)amino]benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide
- N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
- 20 N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-4-iodobenzenesulfonamide
- N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]benzenesulfonamide
- N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-2-naphthalenesulfonamide
- 25 N-[4-[3-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]propyl]-phenyl]-3-quinolinesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
- 30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-isopropylbenzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

- 12 -

- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide
- 5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonamide
- 10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide
- 15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzenesulfonamide
- 20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(1-oxoheptyl)amino]benzenesulfonamide
- 25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(1-oxo-4-phenylbutyl)amino]benzenesulfonamide
- 30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(propoxycarbonyl)amino]benzenesulfonamide
- 132 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[[(fur-2-ylmethyl)amino]carbonyl]amino]benzenesulfonamide
- 137 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[[(2-phenylethyl)amino]carbonyl]amino]benzenesulfonamide
- 142 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[[(2-indol-3-ylethyl)amino]carbonyl]amino]benzenesulfonamide
- 147 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[[(octylamino)carbonyl]amino]benzenesulfonamide
- 152 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[(hexylamino)carbonyl]-5-indolinesulfonamide
- 157 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[(octylamino)carbonyl]-5-indolinesulfonamide
- 162 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[(N-methyl-N-octylamino)carbonyl]-5-indolinesulfonamide
- 167 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(1-oxononyl)-5-indolinesulfonamide
- 172 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-methylthiazol-2-yl)-5-indolinesulfonamide
- 177 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-octylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-ethyl-5-methylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolidinon-1-yl)benzenesulfonamide

5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(4,4,4-trifluorobutyl)-2-imidazolidinon-1-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-phenylpropyl)-2-imidazolidinon-1-yl]benzenesulfonamide

10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(4,4,5,5,5-pentafluoropentyl)-2-imidazolidinon-1-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2-cyclohexylethyl)-2-imidazolidinon-1-yl]benzenesulfonamide

15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-[3-(4-chlorophenyl)propyl]-2-imidazolidinon-1-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-pentyl-2-imidazolidinon-1-yl)benzenesulfonamide

20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2-imidazolidinon-1-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2-cyclopentylethyl)-2-imidazolidinon-1-yl]benzenesulfonamide

25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclohexylpropyl)-2-imidazolidinon-1-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2,2-dimethylhexyl)-2-imidazolidinon-1-yl]benzenesulfonamide

30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolon-1-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(4,4,4-trifluorobutyl)-2-imidazolon-1-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolon-1-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2-imidazolon-1-yl]benzenesulfonamide

- 14 -

- 5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octyl-3-oxo-[1,2,4]-triazol-4-yl)benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexyl-5-tetrazolon-1-yl)benzenesulfonamide
10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octyl-5-tetrazolon-1-yl)benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(3-cyclopentylpropyl)-5-tetrazolon-1-yl]benzenesulfonamide
15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentyloxazol-5-yl)benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octyloxazol-5-yl)benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)oxazol-5-yl]benzenesulfonamide
20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(4-ethyl-5-methylthiazol-2-yl)amino]benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(4,5,6,7-tetrahydrobenzothiazol-2-yl)amino]benzenesulfonamide
25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexylimidazol-4-yl)benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(1-methyl-2-octylimidazol-5-yl)benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[1-methyl-2-(2-cyclopentylethyl)imidazol-5-yl]benzenesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[1-methyl-2-[2-(4-fluorophenyl)ethyl]imidazol-5-yl]benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-3-yl]benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide

- 15 -

- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexylthio-[1,2,4]-triazol-3-yl)benzenesulfonamide
- 5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[4-(4-propylpiperidin-1-yl)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]benzenesulfonamide
- 10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[4-(hexylmethylamino)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]benzenesulfonamide
- 15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[[4-(N-heptyl, N-methylamino)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]benzenesulfonamide
- 20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(1-octyl-2,4-imidazolidinedion-3-yl)benzenesulfonamide
- 25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-nitrophenyl)-5-pyrazolon-1-yl]benzenesulfonamide
- 30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(1-hydroxy-1-hexylheptyl)-5-methyl-[1,2,3]-triazol-2-yl]benzenesulfonamide
- 20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(1-hydroxyheptyl)-5-methyl-[1,2,3]-triazol-2-yl]benzenesulfonamide
- 25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]-2-methylpropyl]-phenyl]-4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonamide
- 30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]-2-methylpropyl]-phenyl]-4-iodobenzenesulfonamide
- 25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]-2-methylpropyl]-phenyl]-4-[(hexylamino)carbonyl]amino]benzenesulfonamide
- 30 N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-4-iodobenzene-sulfonamide
- 20 N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-2-naphthalene-sulfonamide
- 25 N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-quinoline-sulfonamide
- 30 N-[4-[2-[(2-hydroxy-2-(3-chlorophenyl)ethyl)amino]ethyl]phenyl]-3-isopropylbenzenesulfonamide

- 16 -

N-[4-[2-[[2-hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

5 N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]phenyl]-1-[(octylamino)carbonyl]-5-indolinesulfonamide

10 N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolidinon-1-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide

15 N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-cyanophenyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

20 N-[4-[2-[[2-hydroxy-2-(3-cyanophenyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-heptyl-5-methyl-[1,2,3]-triazol-2-yl)benzenesulfonamide

25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2,4-imidazolidinedion-1-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2,4-imidazolidinedion-1-yl)benzenesulfonamide

30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2,4-imidazolidinedion-1-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-pentyl-[1,2,4]-oxadiazol-5-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-[1,2,4]-oxadiazol-5-yl)benzenesulfonamide

- 17 -

- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-heptyl-[1,2,4]-oxadiazol-5-yl)benzenesulfonamide
- 5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-[1,2,4]-oxadiazol-5-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-5-yl]benzenesulfonamide
- 10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-5-yl]benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-pentyl-[1,2,4]-thiadiazol-5-yl)benzenesulfonamide
- 15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-[1,2,4]-thiadiazol-5-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-heptyl-[1,2,4]-thiadiazol-5-yl)benzenesulfonamide
- 20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-[1,2,4]-thiadiazol-5-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(2-cyclopentylethyl)-[1,2,4]-thiadiazol-5-yl]benzenesulfonamide
- 25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-[1,2,4]-thiadiazol-5-yl]benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentyl-[1,2,4]-thiadiazol-3-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexyl-[1,2,4]-thiadiazol-3-yl)benzenesulfonamide
- 30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptyl-[1,2,4]-thiadiazol-3-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octyl-[1,2,4]-thiadiazol-3-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)-[1,2,4]-thiadiazol-3-yl]benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-thiadiazol-3-yl]benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-pentyl-3-oxo-[1,2,4]-triazol-2-yl)benzenesulfonamide

- 18 -

- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexyl-3-oxo-[1,2,4]-triazol-2-yl)benzenesulfonamide
5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-heptyl-3-oxo-[1,2,4]-triazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octyl-3-oxo-[1,2,4]-triazol-2-yl)benzenesulfonamide
10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(2-cyclopentylethyl)-3-oxo-[1,2,4]-triazol-2-yl]benzenesulfonamide
10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(3-cyclopentylpropyl)-3-oxo-[1,2,4]-triazol-2-yl]benzenesulfonamide
15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentyloxazol-2-yl)benzenesulfonamide
15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexyloxazol-2-yl)benzenesulfonamide
20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptyloxazol-2-yl)benzenesulfonamide
20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octyloxazol-2-yl)benzenesulfonamide
25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)oxazol-2-yl]benzenesulfonamide
25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)oxazol-2-yl]benzenesulfonamide
25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-pentyloxazol-2-yl)benzenesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexyloxazol-2-yl)benzenesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-heptyloxazol-2-yl)benzenesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octyloxazol-2-yl)benzenesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(2-cyclopentylethyl)oxazol-2-yl]benzenesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(3-cyclopentylpropyl)oxazol-2-yl]benzenesulfonamide

- 19 -

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexyloxazol-5-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptyloxazol-5-yl)benzenesulfonamide

5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)oxazol-5-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(4-cyclohexylbutyl)oxazol-5-yl]benzenesulfonamide

10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-[2-(4-fluorophenyl)ethyl]oxazol-5-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentyloxazol-4-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexyloxazol-4-yl)benzenesulfonamide

15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptyloxazol-4-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octyloxazol-4-yl)benzenesulfonamide

20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)oxazol-4-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)oxazol-4-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentylthiazol-2-yl)benzenesulfonamide

25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexylthiazol-2-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptylthiazol-2-yl)benzenesulfonamide

30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octylthiazol-2-yl)benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)thiazol-2-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)thiazol-2-yl]benzenesulfonamide

- 20 -

- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-pentylthiazol-2-yl)benzenesulfonamide
5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-heptylthiazol-2-yl)benzenesulfonamide
10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octylthiazol-2-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(2-cyclopentylethyl)thiazol-2-yl]benzenesulfonamide
15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-(3-cyclopentylpropyl)thiazol-2-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentylthiazol-4-yl)benzenesulfonamide
20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexylthiazol-4-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptylthiazol-4-yl)benzenesulfonamide
25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentylthiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexylthiazol-5-yl)benzenesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptylthiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octylthiazol-5-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)thiazol-5-yl]benzenesulfonamide

- 21 -

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)thiazol-5-yl]benzenesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-methylthiazol-2-yl)-5-indolinesulfonamide

5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-pentylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-hexylthiazol-2-yl)-5-indolinesulfonamide

10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-heptylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-octylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(2-cyclopentylethyl)thiazol-2-yl]-5-indolinesulfonamide

15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(3-cyclopentylpropyl)thiazol-2-yl]-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-pentylthiazol-2-yl)-5-indolinesulfonamide

20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-hexylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-heptylthiazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[4-(2-cyclopentylethyl)thiazol-2-yl]-5-indolinesulfonamide

25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[4-(3-cyclopentylpropyl)thiazol-2-yl]-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-methyloxazol-2-yl)-5-indolinesulfonamide

30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-pentyloxazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-hexyloxazol-2-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-heptyloxazol-2-yl)-5-indolinesulfonamide

- 22 -

- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-octyloxazol-2-yl)-5-indolinesulfonamide
5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(2-cyclopentylethyl)oxazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(3-cyclopentylpropyl)oxazol-2-yl]-5-indolinesulfonamide
10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-methyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-pentyloxazol-2-yl)-5-indolinesulfonamide
15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-hexyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-heptyloxazol-2-yl)-5-indolinesulfonamide
20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-octyloxazol-2-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[4-(2-cyclopentylethyl)oxazol-2-yl]-5-indolinesulfonamide
25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[4-(3-cyclopentylpropyl)oxazol-2-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-methyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-pentyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-hexyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-heptyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(3-octyl-[1,2,4]-oxadiazol-5-yl)-5-indolinesulfonamide
35 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[3-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-5-yl]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[3-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-5-yl]-5-indolinesulfonamide

- 23 -

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-methyl-[1,2,4]-oxadiazol-3-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-pentyl-[1,2,4]-oxadiazol-3-yl)-5-indolinesulfonamide

5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-hexyl-[1,2,4]-oxadiazol-3-yl)-5-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-heptyl-[1,2,4]-oxadiazol-3-yl)-5-indolinesulfonamide

10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(5-octyl-[1,2,4]-oxadiazol-5-yl)-3-indolinesulfonamide

N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-3-yl]-5-indolinesulfonamide

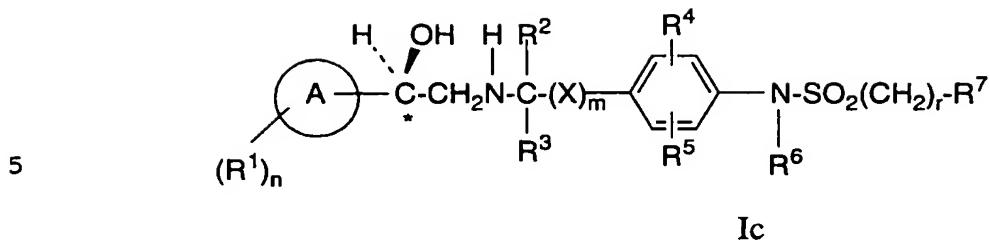
15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]-5-indolinesulfonamide

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in structural Formula I.

Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule, in particular, R² and R³. Each such asymmetric center will produce 20 two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the hydroxy substituent is above the plane of the structure, as seen in Formula Ic, is 25 more active and thus more preferred over the compound in which the hydroxy substituent is below the plane of the structure.

The following stereospecific structure represents the preferred stereoisomers of the instant invention:

- 24 -



where n, m, r, A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and X are as defined above under formula I.

10 Throughout the instant application, the following terms have the indicated meanings:

15 The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

20 The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexaoxy and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

25 Examples of 5 and 6-membered heterocycles and fused heterocycles of A, Z and R^{1a} include pyridyl, quinolinyl, pyrimidinyl, pyrrolyl, thienyl, imidazolyl, thiazolyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzoxazinyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, 30 tetrahydroquinolinyl, furopyridine and thienopyridine.

The preferred values of A and Z are phenyl, naphthyl, benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or

- 25 -

heterocycles with from 1 to 4 heteroatoms independently selected from one of oxygen or sulfur, and/or 1 to 4 nitrogen atoms.

The more preferred values of A are phenyl, pyridyl, quinolinyl, pyrimidinyl, pyrrolyl, thienyl, imidazolyl, and thiazolyl.

The more preferred values of Z are phenyl, naphthyl, quinolinyl, thienyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl,

indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzoxazinyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, triazolyl, tetrazolyl,

oxadiazolyl, imidazolyl, oxazolyl, thiazolyl, imidazolidinyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidyl, pyrazolyl, tetrahydrobenzothiazolyl and tetrahydroquinolinyl. When Z is attached to $-\text{NSO}_2(\text{CH}_2)_r-$, it is

preferably phenyl, naphthyl or a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from

oxygen, sulfur and nitrogen. When Z is part of the definition of R⁸, it is preferably phenyl; a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, a benzene

ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, or a 5 or 6-

membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C₃-C₈ cycloalkyl ring.

The preferred heterocycles of R^{1a} are thienyl, thiadiazolyl, triazolyl, tetrazolyl, oxadiazolyl, imidazolyl, oxazolyl, thiazolyl, imidazolidinyl, pyrazolyl, isoxazolyl, pyridyl, pyrimidyl, and pyrazolyl.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example, NR⁸R⁸ may represent NH₂, NHCH₃, N(CH₃)CH₂CH₃, and the like.

The following abbreviations are used throughout the specification:

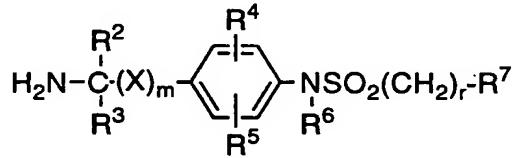
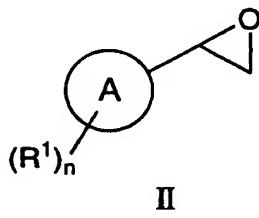
| | |
|--------|---------------------------------|
| Boc | : tert-butyloxycarbonyl |
| Cbz | : carbobenzyloxy |
| DIP-Cl | : diisopinocampheylchloroborane |
| DMF | : dimethylformamide |

- 26 -

| | |
|-------------|---|
| DMSO | : dimethylsulfoxide |
| HPLC | : high pressure liquid chromatography |
| Me | : methyl |
| MPLC | : medium pressure liquid chromatography |
| 5 | |
| Ms | : methanesulfonyl (mesyl) |
| NBS | : N-bromosuccinimide |
| NCS | : N-chlorosuccinimide |
| nHex | : n-hexyl |
| TBAF | : tetrabutylammonium fluoride |
| 10 | |
| TBS (TBDMS) | : t-butyldimethylsilyl |
| TFA | : trifluoroacetic acid |
| THF | : tetrahydrofuran |

The compounds (I) of the present invention can be prepared from epoxide intermediates such as those of formula II and amine intermediates such as those of formula III. The preparation of these intermediates is described in the following schemes.

20



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where n, m, r, A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and X are as defined above.

30

Compounds II are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Acid chloride 1, which may be commercially available or readily prepared from the corresponding acid by treatment with, for example, thionyl chloride or oxalyl chloride, is treated with diazomethane in a solvent such as diethyl ether. The resultant diazoketone is then treated with hydrogen chloride to give chloroketone 2 (X = Cl). The haloketone 2 is then reduced with a reducing agent such as sodium borohydride. The resultant alcohol 3 is

- 27 -

treated with base such as potassium carbonate in refluxing acetone to provide the desired epoxide II. The enantiomerically enriched (*R*) and (*S*) epoxides II are readily available by asymmetric reduction of haloketones 2 using chiral reducing agents such as (-) or (+)-DIP-Cl, (*R*) or (*S*)-Alpine borane or (*R*) or (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole-borane ((*R*) or (*S*)-OAB•BH₃).

SCHEME 1

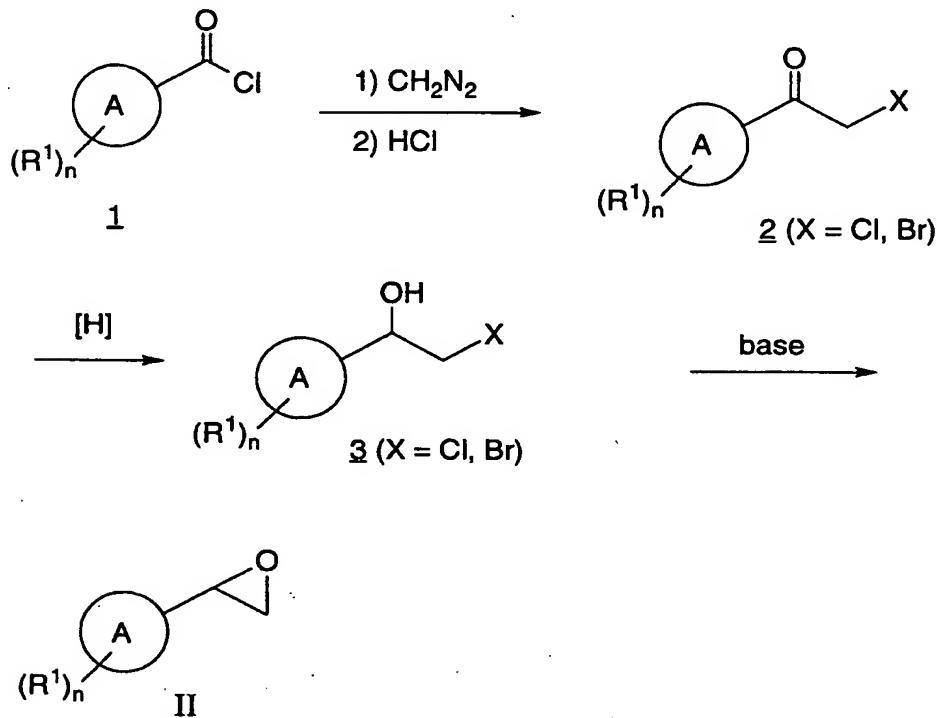
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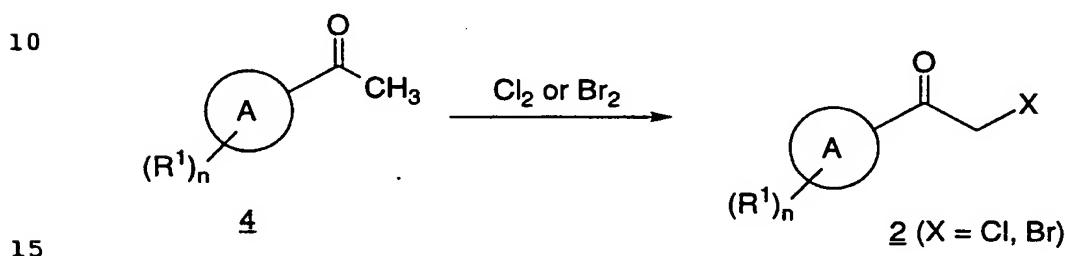


An alternate route to the desired haloketones 2 is illustrated in Scheme 2. Methylketone 4 may be converted to the corresponding haloketone using a variety of reagents known to those in the art and summarized in Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, 369-372. Conveniently, methylketone 4 is treated

- 28 -

with chlorine or *N*-chlorosuccinimide in acetic acid with an additional acid source such as hydrogen chloride or aluminum chloride. For the synthesis of 2 ($X = Br$), bromine, dibromobarbituric acid or NBS with hydrogen bromide or aluminum bromide may be used. In some cases,
 5 the chloro or bromoketones 2 may be commercially available.

SCHEME 2



Many of the methylketones 4 are commercially available or readily prepared by methods described in the literature and known to those skilled in the art. R¹ substituents on the acid chlorides 1 or
 20 methylketones 4 may need to be protected during the subsequent procedures. A description of such protecting groups may be found in: Protective Groups in Organic Synthesis, 2nd Ed., T. W. Greene and P. G. M. Wuts, John Wiley and Sons, New York, 1991.

Compounds III can be conveniently prepared by a variety
 25 of methods familiar to those skilled in the art. A convenient route for their preparation when R⁶ is hydrogen is illustrated in Scheme 3. Compound 5 is selectively protected as a suitable carbamate derivative 6 with, for example, di-*tert*-butyl dicarbonate or carbobenzyloxy chloride. This compound is then treated with a sulfonyl halide, preferably the sulfonyl chloride 7, and a base such as pyridine in an
 30 anhydrous solvent such as dichloromethane or chloroform for 0.5 to 24 hours at temperatures of -20 to 50°C, preferably 0°C, to provide the sulfonamide 8. The protecting group is then removed with, for

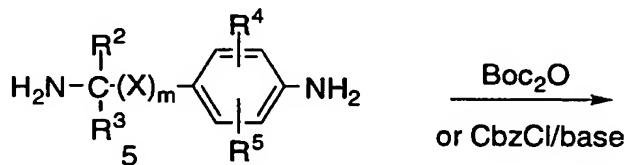
- 29 -

example, trifluoracetic acid in the case of Boc or catalytic hydrogenation in the case of Cbz, to give the desired amine 9.

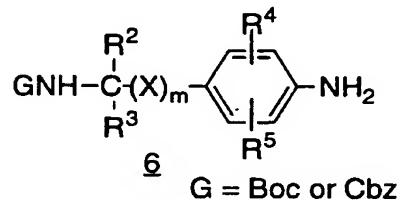
SCHEME 3.

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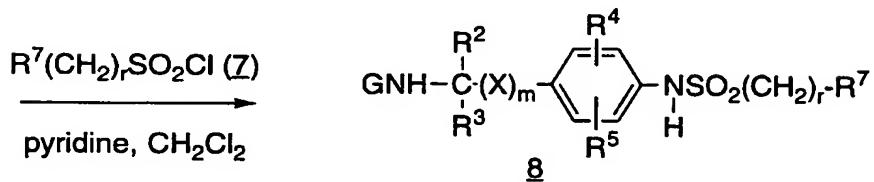
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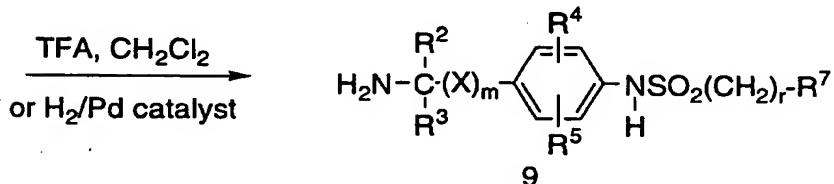
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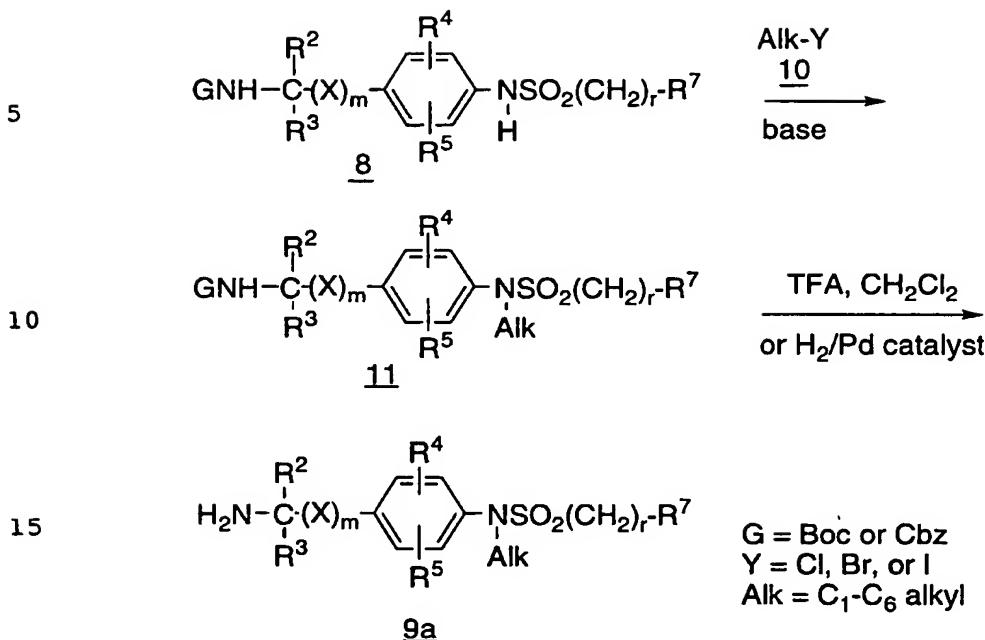


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Compounds III where R⁶ is not hydrogen may be conveniently prepared as illustrated in Scheme 4. Sulfonamide 8, prepared as described above, is alkylated with an appropriate alkylating agent 10 in the presence of base to provide sulfonamide 11. Removal of the protecting group as above gives the desired compound 9a.

- 30 -

SCHEME 4



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The sulfonyl chlorides 7, many of which are commercially available, can also be readily prepared by a number of methods familiar to those skilled in the art. One suitable method involves the addition of an organolithium reagent or a Grignard reagent to sulfonyl chloride following the procedure of S. N. Bhattacharya, *et. al.*, J. Chem. Soc. (C), 1265-1267 (1969). Another convenient method involves the treatment of a thiol with sulfonyl chloride and a metal nitrate according to the procedure of Y. J. Park, *et. al.*, Chemistry Letters, 1483-1486 (1992). Sulfonic acids are also conveniently converted to the corresponding sulfonyl chloride by treatment with PCl_5 , PCl_3 or SOCl_2 (J. March, Advanced Organic Chemistry, 4th Ed., John Wiley and Sons, New York: 1992, p1297 and references cited therein). Aromatic and heteroaromatic compounds may be chlorosulfonylated directly by treatment with Vilsmeier's reagent or chorosulfonic acid (Organic Synthesis, I, 8).

- 31 -

The diamines 5 are commercially available or readily prepared by methods described in the literature or known to those skilled in the art. Compound 5 where R₂ or R₃ is methyl can be prepared from the corresponding amino acid following the method of J. D. Bloom, *et. al.*, *J. Med. Chem.*, 35, 3081-3084 (1992). As illustrated in Scheme 5 for R₃ = methyl, the appropriate (*R*) amino acid 12 is esterified, conveniently by treatment with methanolic hydrochloric acid, and then treated with di-*tert*-butyl dicarbonate to give compound 13.
The ester group is reduced with a hydride source such as lithium borohydride and the resultant alcohol is converted to a leaving group such as a mesylate. Removal of the Boc protecting groups gives diamine 14. This compound is subjected to catalytic hydrogenation in the presence of base such as sodium acetate to give the desired α -methyl amine 15. The other enantiomer is available through an analogous sequence starting with the corresponding (*S*) amino acid.

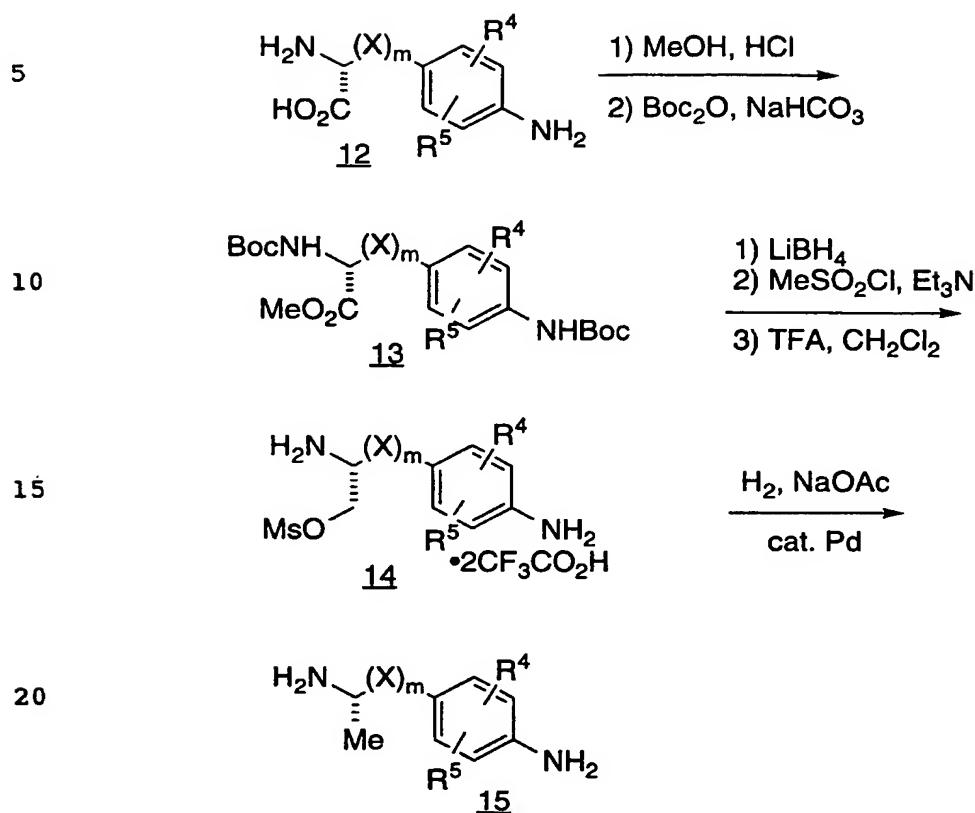
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- 32 -

SCHEME 5



²⁵
 Diamines 5 or sulfonamide amines 9 where X is $-\text{CH}_2\text{O}-$ and m is 1 are also readily prepared by methods described in the literature or known to those skilled in the art. For example, as shown in Scheme 6, the sodium salt of 4-nitrophenol 16 is alkylated with 1-bromo-2-chloroethane, conveniently in refluxing 2-butanone with a base such as potassium carbonate to give chloro derivative 17. The chloride is converted to the corresponding amine by treatment with lithium azide followed by reduction with, for example, triphenylphosphine in aqueous tetrahydrofuran. Protection of the resultant amine, conveniently as its t-butyl carbamate by treatment with di-tert-butyldicarbonate, gives derivative 18. The nitro group is then reduced, for example, by

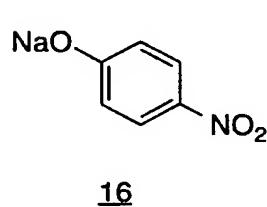
- 33 -

catalytic hydrogenation to provide amine 19. Acylation of intermediate 19 with sulfonyl chloride 7, followed by deprotection with acid such as trifluoroacetic acid gives the desired intermediate 20.

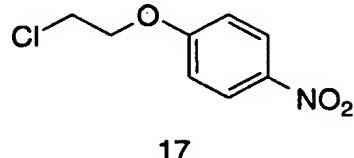
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SCHEME 6

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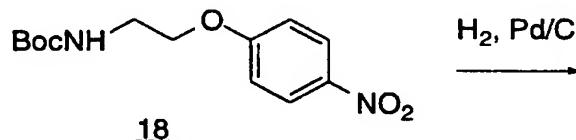


$\xrightarrow{\text{BrCH}_2\text{Cl}}$
 $\xrightarrow{\text{K}_2\text{CO}_3,$
 2-butanone,
 reflux, 24h}

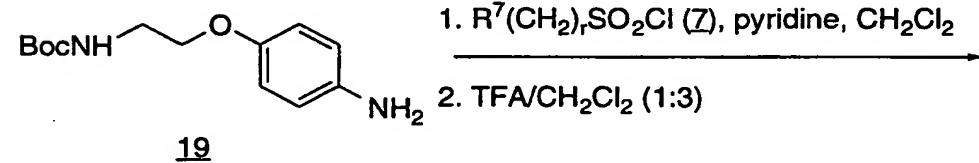


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1. LiN_3 , DMF, 60°
 2. PPh_3 , THF/ H_2O ,
 3. Boc anhydride,
 CH_2Cl_2

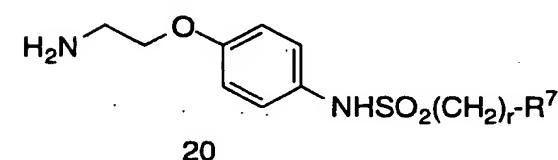


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Alternatively, diamine 5 where X is $-\text{CH}_2\text{O}-$ and m is 1 is available from intermediate 19 by treatment with trifluoroacetic acid. This diamine may then be modified as illustrated in Scheme 3.

- 34 -

Diamines 5 and sulfonamide amines 9 where X is -CH₂CH₂- and m is 1 are also readily prepared by methods described in the literature or known to those skilled in the art. For example, as shown in Scheme 7, bromo derivative 21 is treated with sodium cyanide to provide nitrile 22. The nitro group is selectively reduced by treatment with hydrogen and catalytic palladium to provide amine 23. Amine 23 is acylated with sulfonyl chloride 7 to give the corresponding sulfonamide 24. Reduction of compound 24 with cobalt chloride and sodium borohydride provides the desired amine 25.

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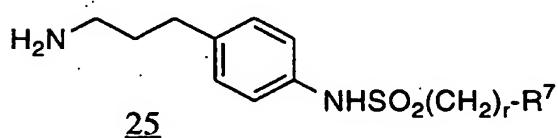
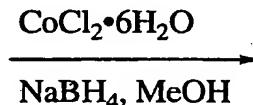
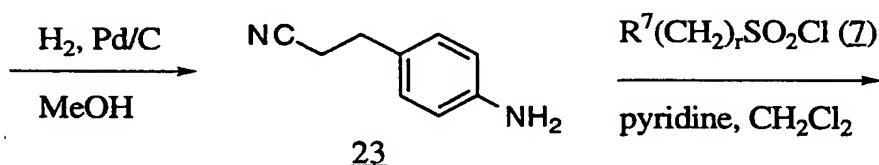
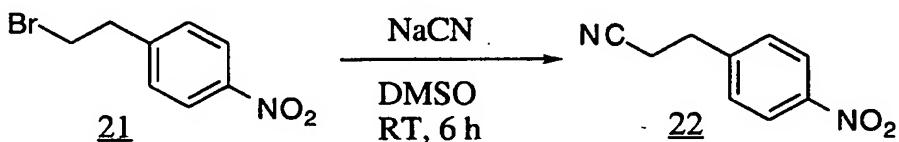
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SCHEME 7



- 35 -

Alternatively, diamine 5 where X is -CH₂CH₂- and m is 1 is available from intermediate 23 by reduction of the nitrile group with, for example, cobalt chloride and sodium borohydride. This diamine may then be modified as illustrated in Scheme 3.

Intermediates II and III are coupled by heating them neat or as a solution in a polar solvent such as methanol, acetonitrile, tetrahydrofuran, dimethylsulfoxide or N-methyl pyrrolidinone for 1 to 24 hours at temperatures of 30 to 150°C to provide compounds I as shown in Scheme 8. The reaction is conveniently conducted in refluxing methanol. Alternatively, a salt of amine III, such as the trifluoroacetate or hydrochloride salt, may be used. In these cases, a base such as sodium bicarbonate or diethylisopropylamine is added to the reaction mixture. The product is purified from unwanted side products by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still, *et. al.*, J. Org. Chem. 43, 2923 (1978), medium pressure liquid chromatography, or HPLC. Compounds which are purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

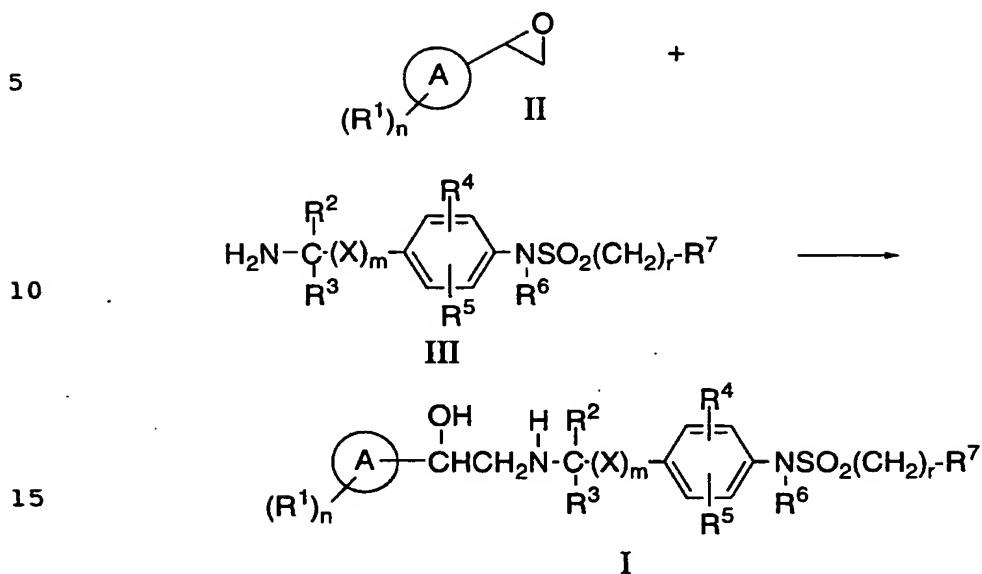
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- 36 -

SCHEME 8

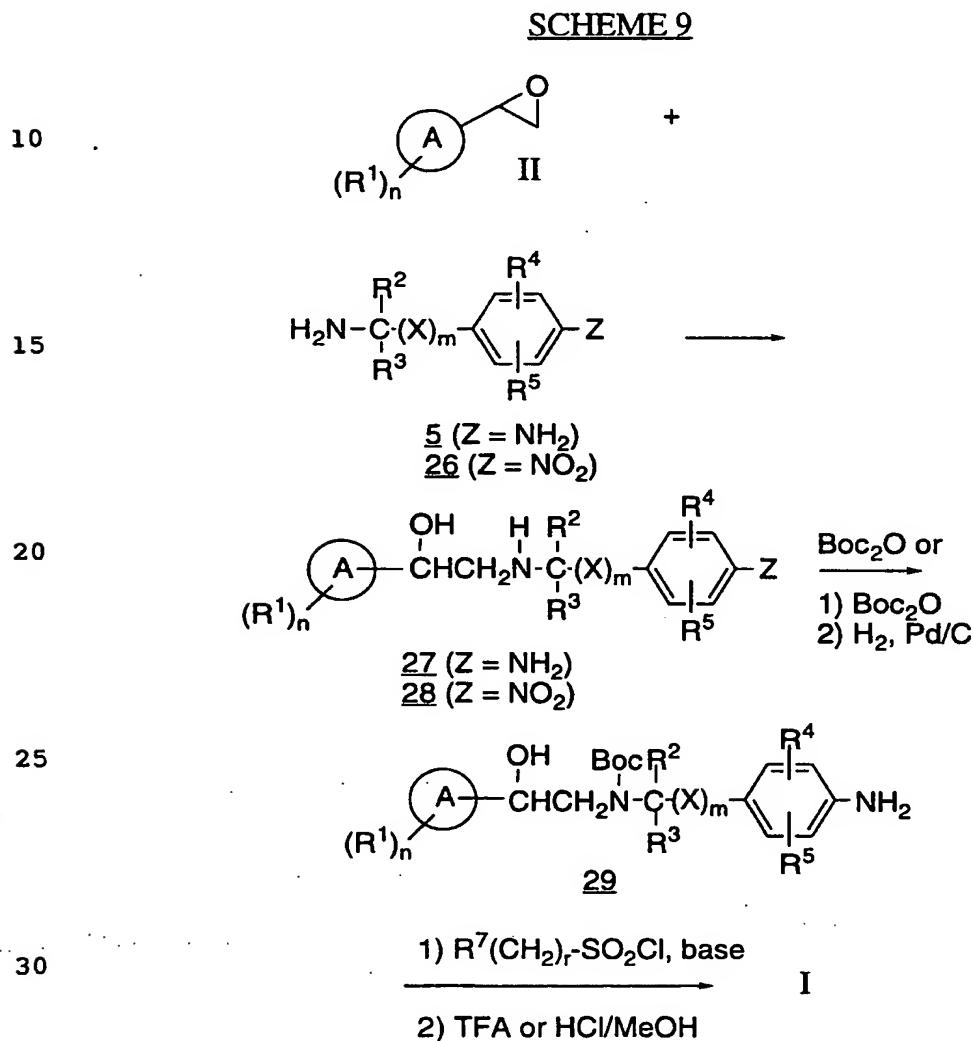


In some cases, the coupling product I from the reaction described in Scheme 8 may be further modified, for example, by the removal of protecting groups or the manipulation of substituents on, in particular, R¹ and R⁷. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

An alternate method for the synthesis of compound I is illustrated in Scheme 9. Epoxide II is coupled to amine 5 as described above for coupling intermediates II and III (Scheme 8) to give aniline derivative 27. The secondary amine is selectively protected, for example, as a carbamate by treatment with di-*tert*-butyldicarbonate to provide carbamate 29. Alternatively, nitro amine 26 is used in the coupling reaction to provide 28. Following protection as described above, the nitro group is reduced, for example, by catalytic hydrogenation with palladium catalyst or raney nickel, to provide intermediate 29. In some cases, other group may be reduced concomitantly. For example, if R¹ is halogen in intermediate 28, it may

- 37 -

be converted to hydrogen in intermediate 29. Treatment with a sulfonyl chloride in the presence of a base such as pyridine followed by removal of the protecting group with, in the case of a *tert*-butylcarbamate, acid such as trifluoroacetic acid or methanolic hydrogen chloride, provides the sulfonamide I.

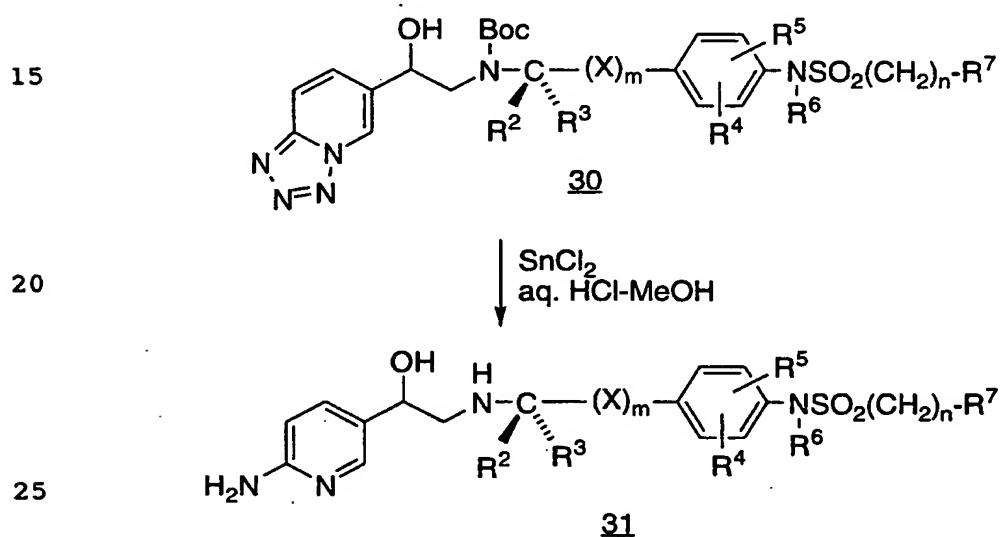


In some cases, compound I from the reaction sequence illustrated in Scheme 9 may be further modified, for example, by the

- 38 -

removal of protecting groups or the manipulation of substituents on, in particular, R1 and R7, as described above. In addition, manipulation of substituents on any of the intermediates in the reaction sequence illustrated in Scheme 9 may occur. One such example is illustrated in Scheme 10. Compound 30, which is prepared as outlined in Scheme 9 from the corresponding epoxide, is subjected to reduction using tin(II) chloride to provide compound 31. Other examples of substituents on compound I which may be reduced to the corresponding amine by methods commonly known to those skilled in the art include nitro groups, nitriles, and azides.

SCHEME 10



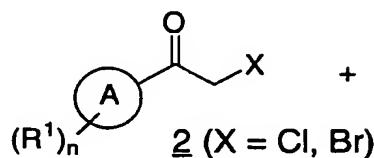
The compounds (I) of the present invention can also be prepared from amine intermediates such as those of formula III and haloketone intermediates such as those of formula 2, as shown in Scheme 11. Amine III is alkylated with haloketone derivative 2, conveniently by treatment of a mixture of III and 2 with base such as potassium carbonate or triethylamine in a polar solvent such as acetonitrile, acetone or dimethylformamide. The resultant aminoketone

- 39 -

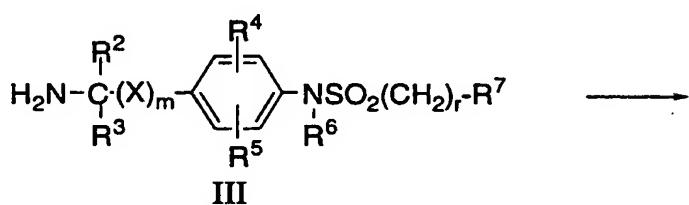
32 is reduced with, for example, sodium borohydride in methanol to give the desired aminoalcohol I.

SCHEME 11

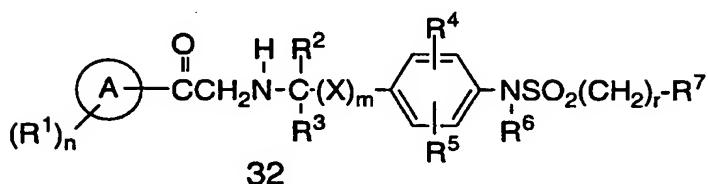
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In some cases, the product I from the reaction described in Scheme 11 may be further modified, for example, by the removal of protecting groups or the manipulation of substituents on, in particular, R¹ and R⁷. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

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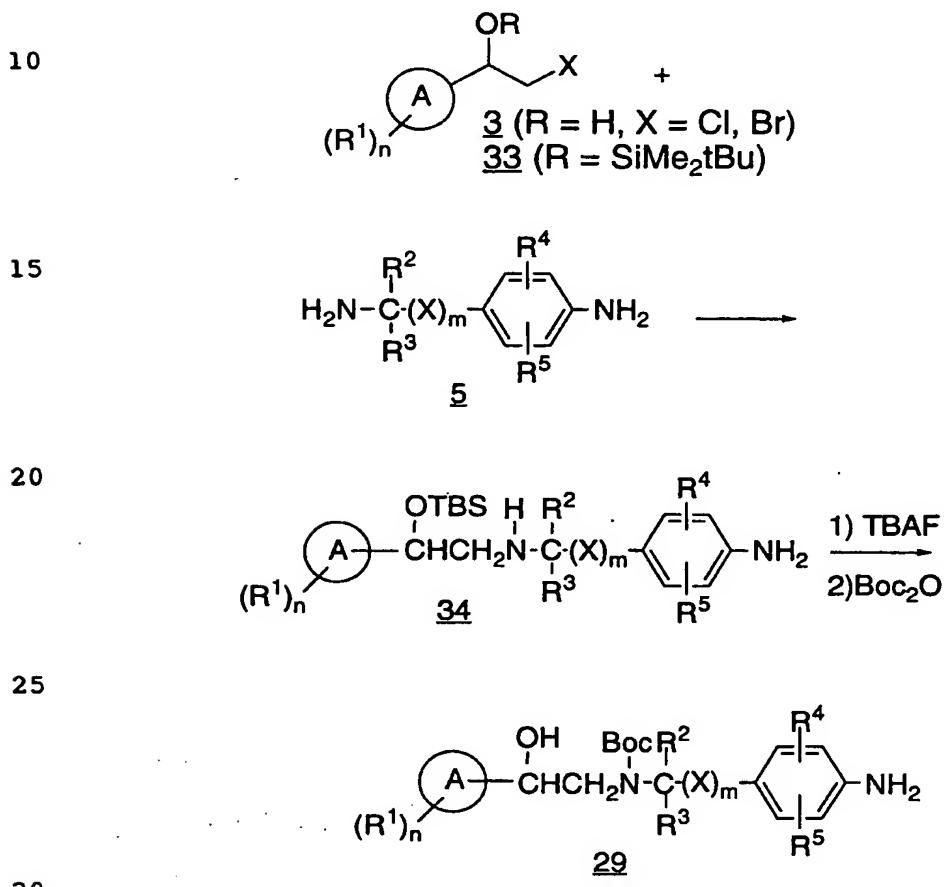
An alternate synthesis of key intermediate 29 is shown in Scheme 12. The alcohol of intermediate 3 is protected, for example, as its t-butyldimethylsilyl ether to give TBS derivative 33. This compound is then treated with amine 5 and a base such as diisopropylethylamine in a solvent, typically polar aprotic such as acetonitrile, at temperatures of

- 40 -

25 to 150 °C for 1 to 72 hours. Typically, an iodide source such as sodium iodide is added to facilitate the reaction. The protecting group is then removed, in the case of silyl ether, by treatment of the resultant amine 34 with a fluoride source such as tetrabutylammonium fluoride.

5 Protection of the secondary amine as before gives key intermediate 29.

SCHEME 12



In some cases, compound I may be synthesized directly from intermediate 27 without protection of the secondary amine. For example, when R² and R³ are both methyl, aniline derivative 27 is treated with sulfonyl chloride 7 and a base such as pyridine in a solvent

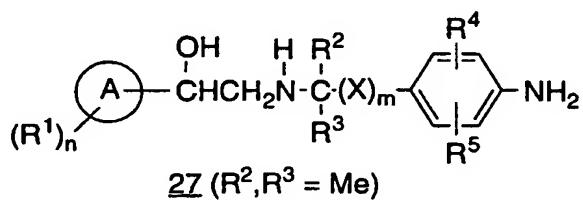
- 41 -

such as dichloromethane at a temperature of -30 to 50 °C, typically 0 °C, to provide compound I.

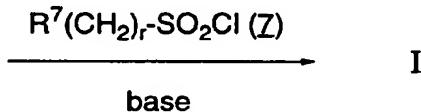
In some cases, the product I from the reaction described in Scheme 13 may be further modified, for example, by the removal of 5 protecting groups or the manipulation of substituents on, in particular, R¹ and R⁷, as described above.

SCHEME 13

10



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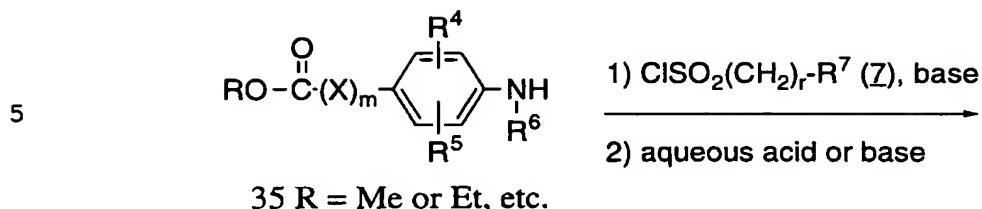
The compounds (I) of the present invention where R² and R³ are hydrogen can also be prepared from acid intermediates of formula 36 and aminoalcohols of formula 37, as shown in Scheme 14. Acid 36 is available from the corresponding ester 35, typically a methyl or ethyl ester, by treatment with sulfonyl chloride Z and a base such as pyridine, followed by hydrolysis of the ester with aqueous acid or base. Acid 36 is coupled to amine 37, which is known in the literature or readily prepared by methods known to those skilled in the art, using a coupling agent such as benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide to provide the amide 38. This is treated with a reducing agent, typically borane, to provide the desired compound I.

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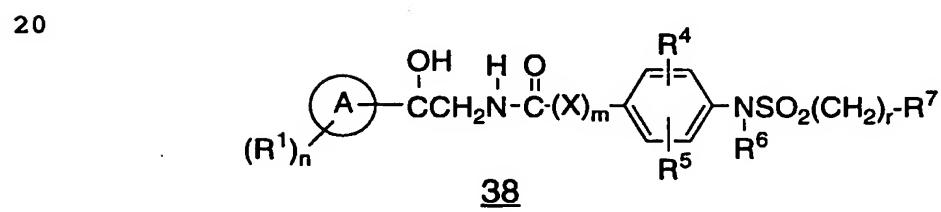
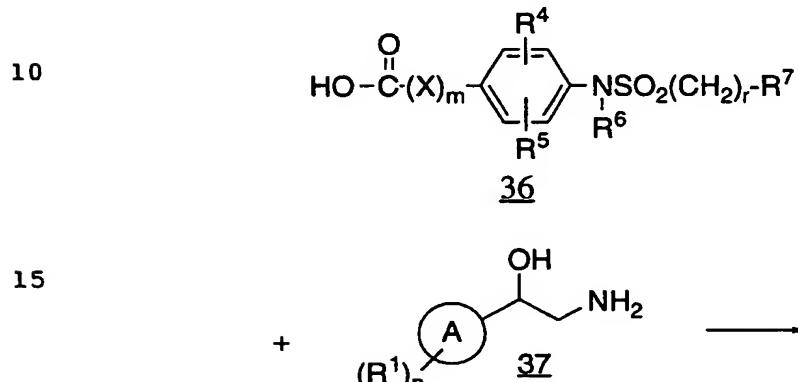
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- 42 -

SCHEME 14



35 R = Me or Et, etc.



25



30 Compounds of the general Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained

- 43 -

may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using 5 optically pure starting materials of known configuration.

The instant compounds can be isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, 10 trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy or tetrazole, can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases. 15

As previously indicated, the compounds of the present invention have valuable pharmacological properties.

The present invention also provides a compound of the general Formula I or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance. 20

In one aspect, the present invention provides a compound of the general Formula I or a pharmaceutically acceptable ester thereof: or a pharmaceutically acceptable salt thereof for use in the treatment of obesity in human or non-human animals.

The present invention further provides a compound of the general Formula I, or a pharmaceutically acceptable ester thereof; or pharmaceutically acceptable salt thereof, for use in the treatment of 25 hyperglycemia (diabetes) in human or non-human animals.

The disease diabetes mellitus is characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels. The result of these 30 defects is elevated blood glucose or hyperglycemia. Research on the treatment of diabetes has centered on attempts to normalize fasting and postprandial blood glucose levels. Treatments have included parenteral

- 44 -

administration of exogenous insulin, oral administration of drugs and dietary therapies.

Two major forms of diabetes mellitus are now recognized.
5 Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes, often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese.
10

In addition the compounds of the present invention lower triglyceride levels and cholesterol levels and raise high density lipoprotein levels and are therefore of use in combatting medical conditions wherein such lowering (and raising) is thought to be beneficial. Thus they may be used in the treatment of hyper-triglyceridaemia, hypercholesterolaemia and conditions of low HDL (high density lipoprotein) levels in addition to the treatment of atherosclerotic disease such as of coronary, cerebrovascular and peripheral arteries, cardiovascular disease and related conditions.
15

Accordingly, in another aspect the present invention
20 provides a method of lowering triglyceride and/or cholesterol levels and/or increasing high density lipoprotein levels which comprises administering, to an animal in need thereof, a therapeutically effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof. In a further aspect the present invention
25 provides a method of treating atherosclerosis which comprises administering, to an animal in need thereof; a therapeutically effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof. The compositions are formulated and administered in the same general manner as detailed below for treating diabetes and obesity. They may also contain other active ingredients known for use in the treatment of atherosclerosis and related conditions, for example fibrates such as clofibrate, bezafibrate and gemfibrozil; inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors for example lovastatin, simvastatin and pravastatin; inhibitors
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- 45 -

of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide; anion exchange resins for example cholestyramine, colestipol or a dialkylaminoalkyl derivatives of a cross-linked dextran; nicotinyl alcohol, nicotinic acid or a salt thereof; vitamin E; and thyromimetics.

The compounds of the instant invention also have the effect of reducing intestinal motility and thus find utility as aiding in the treatment of various gastrointestinal disorders such as irritable bowel syndrome. It has been proposed that the motility of non-sphincteric smooth muscle contraction is mediated by activity at β_3 adrenoreceptors. The availability of a β_3 specific agonist, with little activity at β_1 and β_2 receptors will assist in the pharmacologic control of intestinal motility without concurrent cardiovascular effects. The instant compounds are administered generally as described below with dosages similar to those used for the treatment of diabetes and obesity.

It has also been found unexpectedly that the compounds which act as agonists at β_3 adrenoreceptors may be useful in the treatment of gastrointestinal disorders, especially peptic ulcerations, esophagitis, gastritis and duodenitis, (including that induced by H. pylori), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations.

In addition, β_3 receptors have been indicated to have an effect on the inhibition of the release of neuropeptides in certain sensory fibers in the lung. As sensory nerves may play an important role in the neurogenic inflammation of airways, including cough, the instant specific β_3 agonists may be useful in the treatment of neurogenetic inflammation, such as asthma, with minimal effects on the cardio-pulmonary system.

β_3 adrenoreceptors are also able to produce selective antidepressant effects by stimulating the β_3 receptors in the brain and thus an additional contemplated utility of the compounds of this invention are as antidepressant agents.

- 46 -

The active compounds of the present invention may be orally administered as a pharmaceutical composition, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, which includes sublingual administration, these active compounds may be incorporated with excipients and used in the form of tablets, pills, capsules, ampules, sachets, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated.

When treating diabetes mellitus and/or hyperglycemia generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily

- 47 -

dosage of from 1 milligram to about 1000 milligrams per kilogram of animal body weight, preferably given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 10 milligrams to about 10,000 milligrams, 5 preferably from about 10 milligrams to about 500 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 70 milligrams to about 3500 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

10 The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage 15 unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

20 Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl 25 and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

25 These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

30 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the

- 48 -

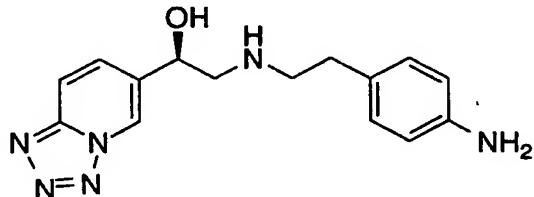
contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The following examples are provided so that the invention might be more fully understood. They should not be construed as limiting the invention in any way.

10

EXAMPLE 1

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(*R*)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)ethylamine

20

A solution of 1.62 g (10 mmol) of (*R*)-2-(tetrazolo[1,5-a]pyrid-6-yl)oxirane (See Fisher and Wyvatt, European Patent Application 0 318 092 A2 for the synthesis of this compound.) and 4.1 g (30 mmol) of 2-(4-aminophenyl)ethylamine in 30 mL of methanol was heated at reflux for 5h. The reaction mixture was concentrated and the residue chromatographed on silica gel (2% methanol/98% methylene chloride) to give 1.69 g (56%) of the title compound: ^1H NMR (400 MHz, CD₃OD) δ 9.01 (d, 1H, J = 1.3 Hz), 8.02 (d, 1H, J = 9.2 Hz), 7.82 (dd, 1H, J = 1.3, 9.2 Hz), 6.94 (d, 2H, J = 6.3 Hz), 6.63 (d, 2H, J = 6.3 Hz), 4.91 (m, 1H), 2.82 (m, 4H), 2.67 (t, 2 H, J = 7.1 Hz).

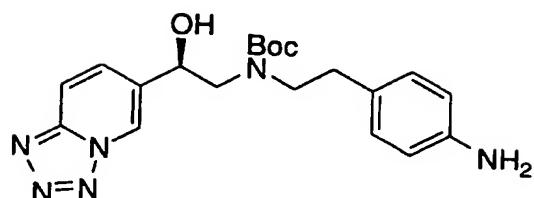
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- 49 -

EXAMPLE 2

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(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)ethylcarbamic acid 1,1-dimethylethyl ester

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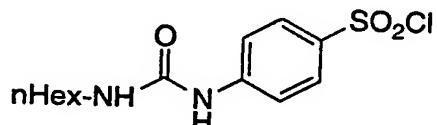
A solution of 1.69 g (56.7 mmol) of the amine from Example 1 and 1.23 g (56.7 mmol) of di-*tert*-butyl dicarbonate in 10 mL of tetrahydrofuran (THF) at 0° C was stirred for 2 h. The reaction mixture was concentrated and the residue chromatographed on silica gel (4% methanol/96% methylene chloride) to afford 2.2 g (97%) of the title compound: ^1H NMR (400 MHz, CD₃OD) δ 8.96 (s, 1H), 8.05 (m, 2H), 7.85 (m, 2H), 6.93 (dd, 2H, J = 7.7, 8.3 Hz), 6.66 (d, 2H, J = 8.3 Hz), 4.99 (m, 1H), 3.49 (m, 4H), 2.70 (t, 2H, J = 6.5 Hz), 1.26 (s, 9H).

15

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EXAMPLE 3

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4-(Hexylaminocarbonylamino)benzenesulfonyl chloride

Hexylamine, 12.15 ml (9.2 mmol), was added dropwise to a solution of 10 ml (9.2 mmol) of phenyl isocyanate in THF (150 ml) at 0°C, and stirring was continued for 1 h. The solvent was removed *in vacuo*, and the resultant hexyl phenyl urea was used without further purification.

A 6-g (2.7 mmol) portion was added over 20 min to chlorosulfonic acid at 0°C, followed by heating at 60°C for 2h. After cooling, the mixture was added to ice/water (100ml) and the aqueous

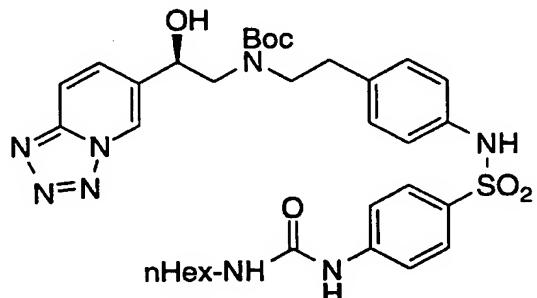
- 50 -

phase extracted with EtOAc (3x100 ml). The combined organic phase was washed with brine (50 ml), dried with MgSO₄, concentrated, and purified by flash chromatography (silica gel, 75% hexane/ 25% ethyl acetate) to give 6 g (70%) of the title compound: ¹H NMR (CDCl₃) δ 5
 7.85 (d, 2H, J = 9.6 Hz), 7.54 (d, 2H, J = 9.6 Hz), 6.79 (br.s, 1H),
 4.71(br. s, 1H), 3.23 (t, 2H, J = 8 Hz), 1.54-1.44 (m, 2H), 1.33-1.20 (m,
 6H), 0.91-0.79 (m, 3H).

EXAMPLE 4

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20 (R)-N-[4-[2-[N-(1,1-dimethylethoxycarbonyl)-N-[2-hydroxy-2-(tetra-
zolo[1,5-a]pyrid-6-yl)]ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbon-
ylamino)benzenesulfonamide

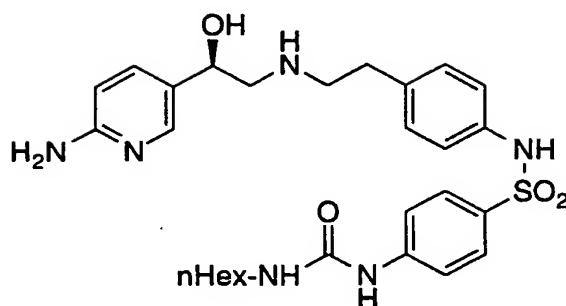
To a stirred solution of 0.200 g (0.502 mmol) of the Boc-compound from Example 2 in 3 mL of methylene chloride was added 25 80 mg (1.00 mmol) of pyridine followed by 0.16 g (0.75 mmol) of the sulfonyl chloride from Example 3. After being stirred for 5h, the reaction mixture was concentrated and the residue chromatographed on silica gel (10% methanol/90% methylene chloride) to afford 0.303 g (88%) of the title compound: ¹H NMR (400 Hz, CD₃OD) δ 8.95 (s, 1H), 8.0-8.08 (m, 1H), 7.75-7.87 (m, 1H), 7.40-7.62 (m, 4H), 7.00 (m, 4H), 4.95 (m, 2H), 3.47 (m, 2H), 3.15 (m, 2H), 2.75 (m, 2H), 1.52 (t, 2H, J = 6.0 Hz), 1.33 (m, 8H), 1.21 (s, 9H), 0.90 (t, 3H, J = 6.0 Hz).

- 51 -

EXAMPLE 5

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(R)-N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

A mixture of 0.302 g (0.44 mmol) of the tetrazine from Example 4, 0.20 g (0.88 mol) of tin(II) chloride dihydrate and 0.3 ml of concentrated aqueous hydrochloric acid in 2 mL of methanol was heated at reflux for 5 h. The reaction mixture was concentrated and the residue purified by reverse-phase MPLC (C8, 47%methanol/53 0.1% trifluoroacetic acid buffer) to give 0.32 g (78%) of the title compound as its bistrifluoroacetate salt: ^1H NMR (400 MHz, CD₃OD) δ 7.96 (dd, 1H, J = 2.0, 9.2 Hz), 7.86 (d, 1H, J = 2.0 Hz), 7.59 (d, 2H, J = 8.8 Hz), 7.43 (d, 2H, J = 8.8 Hz), 7.14 (d, 2H, J = 8.4 Hz), 7.07 (d, 2H, J = 8.4 Hz), 7.03 (d, 1H, J = 9.2 Hz), 4.92 (m, 1H), 3.23 (m, 2H), 3.15 (m, 2H), 2.93 (m, 2H, 4.0 Hz), 1.49 (t, 2H, J = 6.0 Hz), 1.32 (m, 8H), 0.91 (t, 3H, J = 6.0 Hz); CI MS *m/z* 555(M+1).

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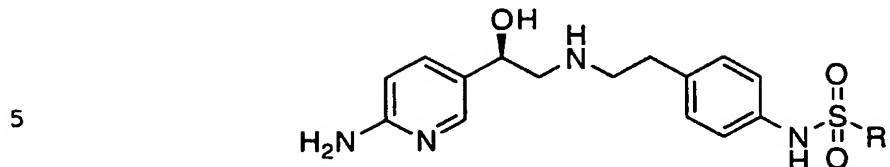
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Following the procedures outlined for Examples 1-5, the compounds listed in Table 1 were prepared.

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- 52 -

TABLE 1

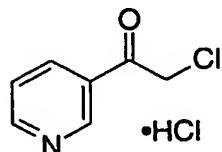


| Example | R | Selected ^1H NMR (CD_3OD) Data |
|---------|--|--|
| 10 6 | Ph, trifluoroacetate salt | 7.74 (m, 2H), 7.53 (m, 1H), 7.45 (m, 2H). |
| 7 | 2-naphthyl, trifluoroacetate salt | 7.93 (m, 4H), 7.75 (d, 1H, $J = 1.7$ Hz), 7.61 (m, 2H) |
| 15 8 | 3-quinolinyl, trifluoroacetate salt | 9.00 (d, 1H, $J = 2.3$ Hz), 8.06 (m, 2H), 7.94 (m, 2H), 7.72 (t, 1H, $J = 7.2$ Hz) |
| 9 | 1,2-benzisoxazol-5-yl, trifluoroacetate salt | 9.02 (s, 1H), 8.30 (d, 1H, $J = 1.3$ Hz), 7.90 (m, 1H), 7.77 (m, 1H) |
| 20 10 | 4-iodophenyl, trifluoroacetate salt | 7.83 (d, 2H, $J = 8.6$ Hz), 7.46 (d, 2H, $J = 8.6$ Hz) |
| 11 | 4-[(N-hexyl,N-methyl- aminocarbonyl)amino]- phenyl, trifluoroacetate salt | 7.62 (d, 2H, $J = 4.6$ Hz), 7.48 (d, 2H, $J = 4.6$ Hz), 2.99 (s, 3H) |
| 25 12 | 4-[(N,N-dimethyl- aminocarbonyl)amino]- phenyl, trifluoroacetate salt | 3.0 (s, 6H) |
| 30 13 | 4-(3-hexyl-2- imidazolidinon-1- yl)phenyl, trifluoroacetate salt | 3.88-3.83 (m, 2H), 3.57-3.50 (m, 2H), 2.89-2.95 (m, 2H), 1.61-1.52 (m, 2H), 1.37-1.30 (m, 6H), and 0.93-0.88 (m, 3H) |

- 53 -

EXAMPLE 14

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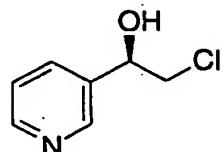
3-(2-Chloroacetyl)pyridine hydrochloride

To a solution of 12 g (11 mL, 100 mmol) of 3-acetylpyridine in 100 mL of ethyl ether was added 100 mL of 1 M ethereal hydrogen chloride. The resultant precipitate was filtered and 15.0 g (95.2 mmol) was collected and placed in a 500-mL round bottom flask equipped with a magnetic stir bar. To this was added 95 mL of 1 M hydrogen chloride in acetic acid. After the mixture was stirred until all the solid had dissolved, 12.7 g (95.2 mmol) of N-chlorosuccinimide (NCS) was added in one portion. The solution turned yellow and the NCS gradually dissolved. After 4 h, a white precipitate had formed. The mixture was allowed to stir for 2.5 days. It was then filtered. The solid collected was washed with 10 mL of acetic acid and 200 mL of ethyl ether to give 15.2 g (83%) of the title compound as a white solid: ¹H NMR (200 MHz, d₆-DMSO) δ 9.22 (t, 1H, J = 1 Hz), 8.29 (dd, 1H, J = 1.6, 5.1 Hz), 8.55 (td, 1H, J = 2, 8.1 Hz), 7.82 (ddd, 1H, J = 0.8, 5.1, 8.1 Hz), 5.27 (s, 2H).

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EXAMPLE 15

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(R)-α-Chloromethyl-3-pyridinemethanol

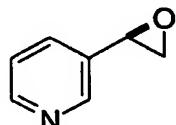
To a stirred solution of 3.67 g (11.5 mmol) of (-)-B-chlorodiisopinocampheylborane [(-)-DIP-Cl] in 11 mL of THF at -25 °C was added a slurry of 1.00 g (5.21 mmol) of the product from

- 54 -

Example 14 in 5 mL of THF via a cannula. Following the addition of 0.80 mL (5.79 mmol) of triethylamine, the reaction mixture was stirred at -25 °C for 4 days. To the mixture was added 10 mL of water which was then allowed to warm to room temperature. To the mixture was added 20 mL of ethyl acetate and the organic phase separated. The aqueous phase was neutralized with saturated NaHCO₃ solution then extracted six times with ethyl acetate. The combined organic phase was concentrated in vacuo to afford a yellow oil. Flash chromatography (silica gel, 75 - 100% ethyl acetate-hexanes) afforded 561 mg (68%) of the title compound as a pale yellow oil: ¹H NMR (400 MHz, CD₃OD) δ 8.58 (d, 1H, J = 1.8 Hz), 8.46 (dd, 1H, J = 4.9, 1.5 Hz), 7.90 (d, 1H, J = 7.9 Hz), 7.44 (dd, 1H, J = 7.9, 4.9 Hz), 4.93 (m, 1H), 3.75 (m, 2H).

EXAMPLE 16

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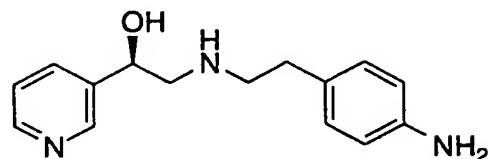
(R)-(Pyrid-3-yl)oxirane

To a solution of 557 mg (3.55 mmol) of the product from Example 15 in 16 mL of acetone was added 1.80 g of potassium carbononate. The mixture was heated at reflux for 20 h then cooled to room temperature. The mixture was filtered and the filtrate evaporated in vacuo. Flash chromatography (silica gel, 2% methanol-methylene chloride) afforded 262 mg (61%) of the title compound as a pale yellow oil: ¹H NMR (200 MHz, CDCl₃) δ 8.54 (m, 2H), 7.52 (m, 1H), 7.24 (m, 1H), 3.86 (dd, 1H, J = 4.0, 2.5 Hz), 3.17 (dd, 1H, J = 5.4, 4.0 Hz), 2.80 (dd, 1H, J = 5.4, 2.5 Hz).

- 55 -

EXAMPLE 17

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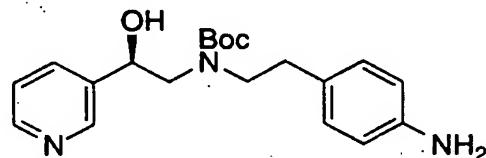


(R)-N-[2-[4-(Aminophenyl)]ethyl]-2-hydroxy-2-(pyrid-3-yl)ethylamine

To a stirred solution of 377 mg (2.44 mmol) of 4-aminophenethylamine in 10 mL of methanol was added a solution of 300 mg (2.48 mmol) of the product from Example 16 in 15 mL of methanol. The mixture was heated at reflux for 16 h then cooled to room temperature. The methanol was removed in vacuo and the residue chromatographed (silica gel, 6 - 8% methanol, 1% ammonia-methylene chloride) to afford 101 mg (16%) of the title compound together with 279 mg of a mixture that was rechromatographed (5% methanol, 1% ammonia-methylene chloride) to give a further 54 mg (9%) of the title compound as an off-white solid: ^1H NMR (500 MHz, CD₃OD) δ 8.52 (d, 1H, J = 1.8 Hz), 8.43 (dd, 1H, J = 4.8, 1.4 Hz), 7.81 (m, 1H), 7.40 (m, 1H), 6.95 (d, 2H, J = 8.3 Hz), 6.67 (d, 2H, J = 8.3 Hz), 4.81 (m, 1H), 2.90-2.65 (m, 6H).

EXAMPLE 18

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(R)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(pyrid-3-yl)ethylcarbamic acid 1,1-dimethylethyl ester

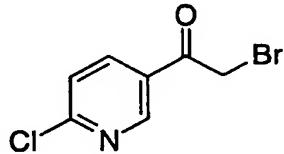
A solution of 386 mg (1.77 mmol) of di-*tert*-butyl dicarbonate in 3.5 mL of THF was added, via a cannula, to a stirred slurry of 456 mg (1.77 mmol) of the product from Example 17 in 3.6

- 56 -

- mL of THF cooled to 0 °C. The yellow solution was stirred at 0 °C for 3 h, then the THF was removed in vacuo. Flash chromatography (silica gel, 10% methanol, 1% ammonia-methylene chloride) afforded 549 mg (87%) of the title compound as an off white solid: ¹H NMR (500 MHz, CD₃OD, mixture of rotomers) δ 8.45 (m, 2H), 7.83 (d, 0.6H, J = 7.4 Hz), 7.78 (d, 0.4H, J = 6.9 Hz), 7.41 (m, 1H), 6.94 (d, 0.8H, J = 8.0 Hz), 6.89 (d, 1.2H, J = 7.8 Hz), 6.66 (d, 2H, J = 7.3 Hz), 4.89 (m, 1H), 3.42-3.21 (m, 4H), 2.67 (m, 2H), 1.39 (s, 5.4H), 1.36 (s, 3.6H).
- 5 An alternative synthesis of the aniline derivative in Example 18 is illustrated in Examples 19-23:
- 10

EXAMPLE 19

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20 2-Chloro-5-(2-bromoacetyl)pyridine hydrochloride

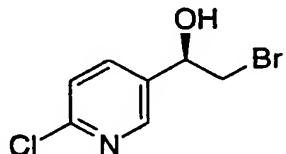
- A solution of 784 mg of 2-chloro-5-acetylpyridine in 10 mL of THF was added via canula to a solution of 1.44 g of dibromobarbituric acid (DBBA) in 10 mL of THF. The resultant solution was heated at 50-55 °C for 12 h, and then an additional 0.72 g DBBA was added. After stirring at 50-55 °C for 2.5 more hours, 0.36 g DBBA was added. The mixture was allowed to stir for 2 h at which point NMR analysis of an aliquot indicated 87% conversion. The reaction mixture was cooled, diluted with ethyl acetate, washed with two portions of saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate and concentrated. Purification by flash chromatography (silica gel, 15% ethyl acetate/hexane) provided 0.86 g (73%) of the title compound as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.96 (d, 1H, J = 2.6 Hz), 8.21 (dd, 1H, J = 2.5, 8.3 Hz), 7.46 (d, 1H, J = 8.4 Hz), 4.37 (s, 2H). The NMR also indicated the presence
- 25
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- 57 -

of the corresponding 2-bromo derivative. The ~4:1 mixture was carried on through the synthesis.

EXAMPLE 20

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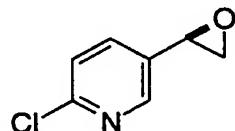
10

(R)- α -Bromomethyl-3-(6-chloropyridine)methanol

To a solution of 602 mg (1.88 mmol) of (-)-DIP-Cl in 0.5 mL of THF at -25 °C was added via canula 200 mg of ketone from Example 19 in 1.5 mL of THF at -25 °C. The reaction mixture was allowed to stir at -25 °C for 17 h. It was then quenched by the addition of water and extracted with ether. The ether phase was diluted with ethyl acetate, washed with two portions of saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate and concentrated. Purification by flash chromatography (silica gel, 15 and 25% ethyl acetate/hexane) gave 170 mg (84%) of the title compound: ^1H NMR (400 MHz, CDCl_3) δ 8.38 (d, 1H), 7.70 (dd, 1H), 7.32 (d, 1H), 4.97 (m, 1H), 3.61 (dd, 1H), 3.50 (dd, 1H), 2.85 (d, 1H).

EXAMPLE 21

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(R)-(2-chloropyrid-5-yl)oxirane

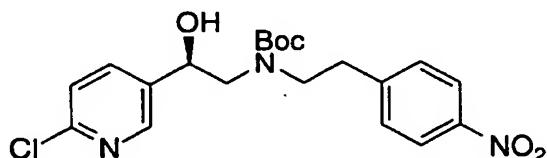
To a solution of 100 mg of bromoalcohol from Example 20 in 2 mL of 1:1 THF:water was added 1 mL of 5 N aqueous sodium hydroxide solution. The mixture was allowed to stir for 10 min. It was then extracted with three portions of dichloromethane. The combined

- 58 -

organic phases were washed with two portions of water and brine, dried over magnesium sulfate, and concentrated to give 98 mg (93%) of the title compound which was used without further purification: ¹H NMR (400 MHz, CDCl₃) δ 8.34 (d, 1H), 7.48 (dd, 1H), 7.29 (d, 1H), 3.86
 5 (dd, 1H), 3.18 (dd, 1H), 2.78 (dd, 1H).

EXAMPLE 22

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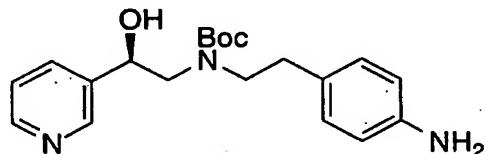
(*R*)-N-[2-[4-(Nitrophenyl)]ethyl]-2-hydroxy-2-(2-chloropyrid-5-yl)ethylcarbamic acid 1,1-dimethylethyl ester

20

Following the procedure outlined in Examples 17 and 18, the title compound was prepared from the epoxide from Example 21 and 4-nitrophenylethylamine: ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, 1H, J = 1.3 Hz), 8.13 (d, 2H, J = 8.6 Hz), 7.66 (br m, 1H), 7.30 (d, 2H, J = 8.1 Hz), 7.27 (br m, 1H), 4.94 (br m), 3.38 (br m, 4H), 2.84 (br m, 2H), 1.40 (s, 9H).

EXAMPLE 23

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(*R*)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(pyrid-3-yl)ethylcarbamic acid 1,1-dimethylethyl ester

To a solution of 80 mg (0.19 mmol) of the nitro compound from Example 22 in 2 mL of ethanol was added 0.114 mL (0.57 mmol) of 5 N aqueous sodium hydroxide solution and 20 mg of raney nickel.

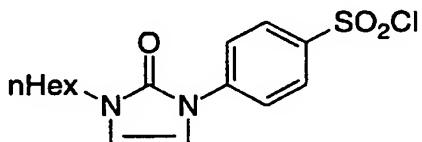
- 59 -

The reaction mixture was shaken at room temperature under 45 psi hydrogen for 16 h. The mixture was neutralized with saturated aqueous sodium phosphate monobasic and extracted with three portions of ethyl acetate. The combined organic phases were washed with water and
 5 brine, dried (magnesium sulfate), and concentrated to give 40 mg (59%) of the title compound which was identical to the sample prepared in Example 18.

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EXAMPLE 24

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4-(3-Hexyl-2-imidazolone-1-yl)phenylsulphonyl chloride

Hexyl iodide (50mmol, 7.38ml) was added to a mixture of 2-amino acetaldehyde dimethyl acetal (100mmol, 11ml) and potassium carbonate (50mmol, 6.9g) in DMF (10ml) at 0°C. Stirring was continued for 16h before diluting with ethyl acetate (200ml), and filtering the solution through a plug of celite. Concentration *in vacuo* was followed by column chromatography (eluant ethyl acetate) to give N-hexyl 2-amino acetaldehyde dimethyl acetal (7.39g, 78%) as a colourless oil.

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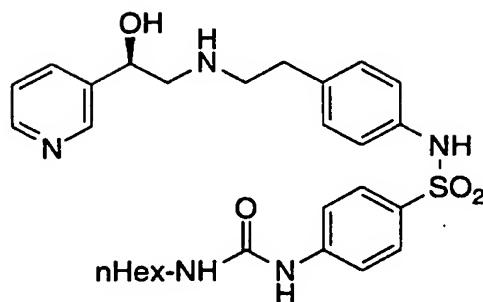
To the amine (38.6mmol, 7.3g) in methylene chloride (100ml) at 0°C was added 4-(chlorosulphonyl) phenyl isocyanate (38.6mmol, 8.4g). The reaction mixture was stirred for 20mins until a clear solution had formed, and 1:1 water: trifluoroacetic acid (100ml total) was added. Vigorous stirring was continued for 16h., the layers separated, the organic layer was diluted with ethyl acetate (500ml) and washed with saturated sodium bicarbonate solution (4x50ml), brine (50ml), dried with anhydrous magnesium sulphate, and concentrated *in vacuo*. Column chromatography (eluant 3 hexane/ 1 ethyl acetate) yielded the title compound as pale yellow crystals (8.8g, 67%).

- 60 -

EXAMPLE 25

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(R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

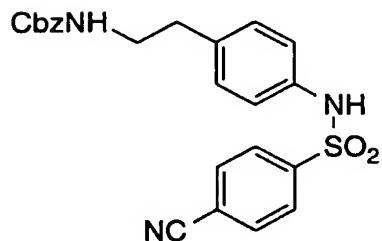
To a solution of 302 mg (0.845 mmol) of the product from Example 18 and 137 mL (1.69 mmol) of pyridine in 10 mL of methylene chloride was added 296 mg (0.928 mmol) of 4-(hexylaminocarbonylamino)benzenesulfonyl chloride from Example 3. The reaction was stirred for 12 h then the solvent removed in vacuo. Flash chromatography (silica gel, 6% methanol, 0.5% ammonia-methylene chloride) afforded 468 mg (87%) of the BOC-protected title compound.

A solution of 468 mg (0.731 mmol) of BOC-protected title compound in 5 mL of methylene chloride and 5 mL of trifluoroacetic acid was stirred for 30 min then the volatile components removed in vacuo. The residue was azeotroped twice with 10% methanol/toluene, twice with methanol, then dried in vacuo to give 521 mg (93%) of the title compound as its trifluoracetate salt: ^1H NMR (400 MHz, CD₃OD) δ 8.88 (s, 1H), 8.79 (d, 1H, J = 5.5 Hz), 8.53 (d, 1H, J = 8.2 Hz), 7.99 (m, 1H), 7.59 (dd, 2H, J = 6.9, 1.9 Hz), 7.43 (dd, 2H, J = 6.9, 1.9 Hz), 7.15 (dd, 2H, J = 8.6, 2.1 Hz), 7.08 (dd, 2H, J = 8.6, 2.1 Hz); 5.23 (m, 1H), 3.40-3.10 (m, 6H), 2.94 (m, 2H), 1.49 (m, 2H), 1.32 (m, 6H), 0.90 (m, 2H).

- 61 -

EXAMPLE 26

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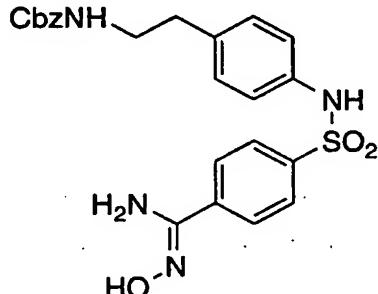
- 10 (N)-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]-4-cyanobenzensulfonamide

Following the procedure outlined in Example 4, the title compound was prepared from 2-(4-aminophenyl)ethylcarbamic acid phenylmethyl ester (see Fisher, et. al., Eur. Pat. Appl. 0 611 003 A1, 15 1994) and 4-cyanobenzenesulfonyl chloride: ^1H NMR (400 MHz, CD₃OD) δ ^1H NMR (400 MHz, CDCl₃) δ 7.81 (d, 2H, J=8.7Hz), 7.69 (d, 2H, J=8.7Hz), 7.32 (m, 5H), 7.06 (d, 2H, J=8.4Hz), 6.96 (d, 2H, J=8.4Hz), 6.75 (s, 1H), 5.06 (s, 2H), 4.71 (t, br, 1H), 3.38 (q, 2H, J=6.9Hz), 2.74 (t, 2H, J=7.0Hz).

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EXAMPLE 27

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- (N)-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]-4-aminooximidomethylbenzensulfonamide

A mixture of the nitrile from Example 26 (2.71g, 6.23mmol), absolute ethanol (65ml), finely divided K₂CO₃ (5.17g,

- 62 -

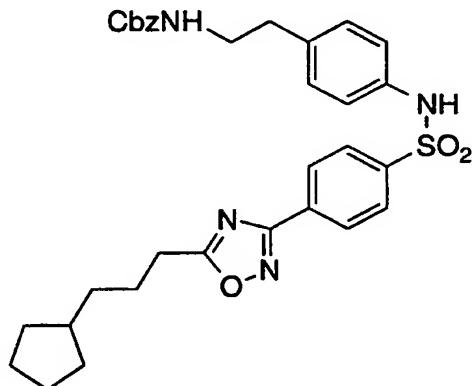
37.4mmol), and hydroxylamine hydrochloride (2.17g, 31.2mmol) was refluxed for 6 h. The ethanol was removed under reduced pressure. The resulting solid was dissolved in ethyl acetate and washed with water 3 times. The organic phase was concentrated in vacuo to 2.87g (98%) of the title compound as a white powder which was of sufficient purity to be used in subsequent steps: ^1H NMR (400 MHz, CD₃OD) δ 7.71 (s, 4H), 7.31 (m, 5H), 7.04 (d, 2H, J=8.4Hz), 6.99 (d, 2H, J=8.4Hz), 5.02 (s, 2H), 3.25 (t, 2H, J=6.8Hz), 2.67 (t, 2H, J=6.7Hz).

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EXAMPLE 28

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(N)-[4-[2-[(phenylmethoxycarbonyl)amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzenesulfonamide

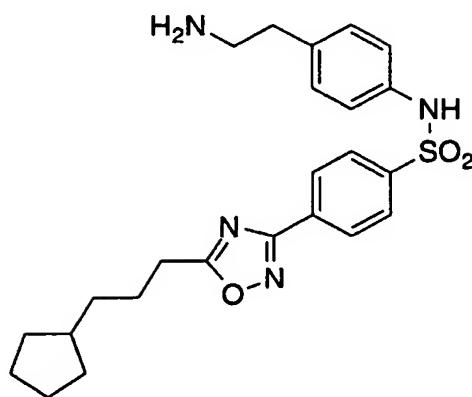
To a solution of compound from Example 27 (0.468g, 1.00mmol) in dry pyridine (5.0ml) was added 4-cyclopentylbutyryl chloride (0.175g, 1.00mmol). The mixture was refluxed for 3.5 h. The pyridine was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (35% ethyl acetate in hexanes) to give 0.152g (26%) of the title compound: ^1H NMR (400 MHz, CDCl₃) δ 8.12 (d, 2H, J=8.7Hz), 7.81 (d, 2H, J=8.7Hz), 7.31 (m, 5H), 7.03 (d, 2H, J=8.1Hz), 6.97 (d, 2H, J=8.4Hz), 6.67 (s, 1H), 5.05 (s, 2H), 4.70 (t, br, 1H), 3.37 (q, 2H, J=6.5Hz), 2.91 (t, 2H, J=7.6Hz), 2.72 (t, 2H, J=7.0), 1.90-1.70 (m, 5H), 1.65-1.30 (m, 6H), 1.06 (m, 2H).

- 63 -

EXAMPLE 29

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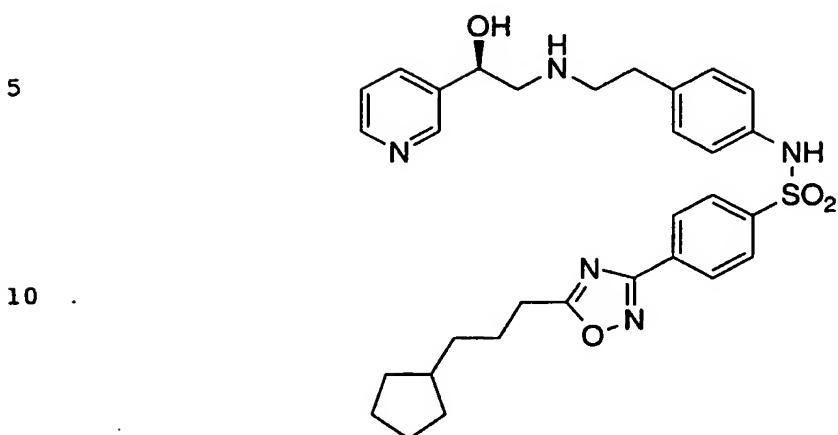
15 N-[4-(2-aminoethyl)phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-
oxadiazol-3-yl]benzenesulfonamide

A mixture of Cbz amine from Example 28 (0.145g, 0.246mmol), palladium hydroxide on carbon (0.02g), and glacial acetic acid (5.0ml) was hydrogenated for 2 h. The acetic acid was removed under reduced pressure. The residue was purified by silica gel chromatography (1 : 9 of 10% ammonium hydroxide in methanol : methylene chloride) to give 0.058g (52%) of the title compound: ^1H NMR (400 MHz, CD₃OD) δ 8.11 (d, 2H, J=8.6Hz), 7.87 (d, 2H, J=8.5Hz), 7.06 (d, 2H, J=8.6Hz), 7.02 (d, 2H, J=8.7Hz), 2.97 (t, 2H, J=7.5Hz), 2.84 (t, 2H, J=6.9Hz), 2.67 (t, 2H, J=7.5Hz), 1.90-1.75 (m, 5H), 1.70-1.40 (m, 6H), 1.12 (m, 2H).

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- 64 -

EXAMPLE 30



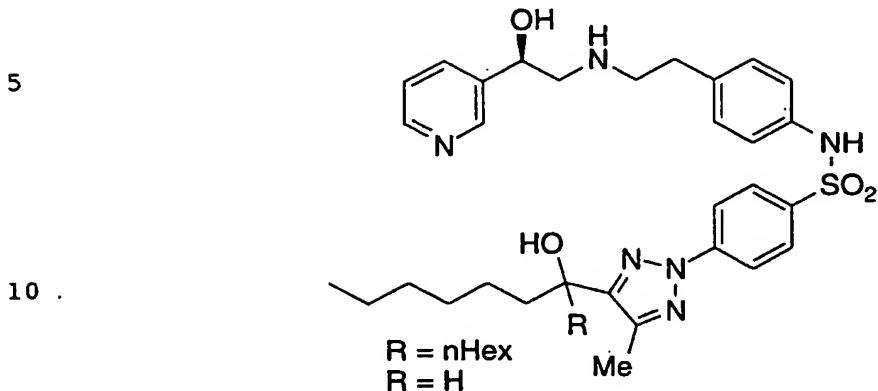
- 15 **(R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzensulfonamide**

To a solution of amine from Example 29 (0.053g, 0.117mmol) in dry methanol (30.0ml) was added 3-pyridine epoxide from Example 16 (0.021g, 0.175mmol). The resulting solution was

20 refluxed overnight. After concentration, the residue was purified by silica gel chromatography (13% methanol in methylene chloride) to give 0.01g (15%) of the title compound: ^1H NMR (400 MHz, CD₃OD) δ 8.52 (d, 1H, J=1.9Hz), 8.42 (dd, 1H, J=1.5, 4.8Hz), 8.13 (d, 2H, J=8.6Hz), 7.85 (m, 3H), 7.40 (dd, 1H, J=4.8, 7.8Hz), 7.10 (d, 1H, J=8.6Hz), 7.03 (d, 2H, J=8.6Hz), 4.81 (dd, 1H, J=4.9, 8.1Hz), 2.96 (t, 2H, J=7.5Hz), 2.93-2.70 (m, 6H), 1.90-1.72 (m, 5H), 1.68-2.48 (m, 4H), 1.42 (m, 2H), 1.11 (m, 2H).

- 65 -

EXAMPLE 31



(*R*)-N-[4-[2-[(2-Hydroxy-2-(pyridin-3-yl)ethyl)amino]ethyl]phenyl]-4-[4-(1-hydroxy-1-hexylheptyl)-5-methyl-[1,2,3]-triazol-2-yl]benzenesulfonamide and (*R*)-N-[4-[2-[(2-Hydroxy-2-(pyridin-3-yl)ethyl)amino]ethyl]phenyl]-4-[4-(1-(*R,S*)-hydroxyheptyl)-5-methyl-[1,2,3]-triazol-2-yl]benzenesulfonamide

To a solution of 180 mg of (*R*)-N-[4-[2-[(2-Hydroxy-2-(pyridin-3-yl)ethyl)amino]ethyl]phenyl]-4-(4-methoxycarbonyl-5-methyl-[1,2,3]-triazol-2-yl)benzenesulfonamide (prepared according to the procedures outlined in examples 14-19) in 2 mL of distilled THF under argon at 0°C was added, dropwise, 2 mL of a 2.0M solution of n-hexylmagnesium bromide in ether. After 5 min, the reaction was quenched with cautious addition of 5 mL of aqueous ammonium chloride followed by ethyl acetate extraction of the aqueous layer. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo to yield the crude products. Preparative layer chromatography (PLC) on 2X0.5 mm thick silica gel plates eluted in 9:1 (v/v) dichloromethane:methanol gave two bands A (20 mg) and B (60mg). ¹H NMR (500 MHz, CD₃OD) of A: δ 8.51 (d, 1H, J=2 Hz), 8.41 (dd, 1H, J=1.5, 5 Hz), 8.01 (dd, 2H, J=2.5, 6.5Hz), 7.81 (m, 1H), 7.78 (dd, 2H, J=2.0, 9.0 Hz), 7.37 (m, 1H), 7.07;7.02 (ABq, 4H, J_{ab}=8.5 Hz), 4.86 (s, CD₃OH), 4.79 (dd, 1H, J= 7.5, 8 Hz), 2.9-2.7 (m, 6H), 2.44 (s, 3H), 1.85 (m, 4H), 1.40-1.15 (m, 16H), 0.83 (t, 6H, J=7 Hz)

- 66 -

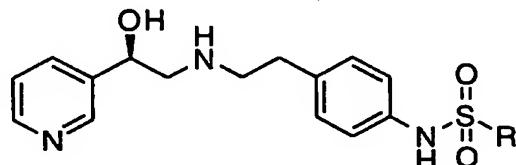
indicating the dihexyl tertiary alcohol adduct, mass spec. expected 677 found 677. ^1H NMR (500 MHz, CD₃OD) of B: 8.51 (d, 1H, J=2 Hz), 8.41 (dd, 1H, J=1.5, 5 Hz), 8.03 (d, 2H, J=9 Hz), 7.78 (d, 2H, J=9 Hz), 7.37 (dd, 1H, J= 4.8, 7.7 Hz), 7.07;7.02 (ABq, 4H, Jab=8 Hz), 4.86 (s, 5 CD₃OH), 4.80 (m, 2H), 2.9-2.7 (m, 6H), 2.38 (s, 3H), 1.87 (m, 2H), 1.44 (m, 1H), 1.4-1.2 (m, 7H), 0.87 (t, 3H, J=7 Hz) indicating the mono-hexyl adduct. Mass spec expected 591 (for the hexyl ketone) found 593 (hexyl alcohol, intermediate ketone reduced by Grignard reagent in situ).

10

Following the procedures outlined for Examples 14-31, the compounds listed in Table 2 were prepared.

TABLE 2

15



20

| Example | R | Selected ^1H NMR (CD ₃ OD) Data |
|---------|-------------------|--|
| 32 | 4-isopropylphenyl | 7.64 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.0 Hz), 4.80 (m, 1H), 2.95-2.70 (m, 7H), 1.22 (d, 6H, J = 6.7 Hz) |
| 25 | 33 | 7.84 (d, 2H, J = 8.6 Hz), 7.47 (d, 2H, J = 8.6 Hz), 5.19 (dd, 1H, J = 10.1, 3.0 Hz), 3.40-3.20 (m, 4H), 2.96 (m, 2H) |
| 30 | 34 | 8.28 (s, 1H), 7.94 (m, 3H), 7.72 (dd, 1H, J = 8.7, 1.9 Hz), 7.60 (m, 2H) |
| | 35 | 9.01 (d, 1H, J = 2.3 Hz), 8.76 (d, 1H, 1.8 Hz), 8.08 (d, 1H, J = 8.7 Hz), 8.04 (d, 1H, J = 8.0 Hz), 7.93 (m, 1H), 7.73 (m, 1H) |

- 67 -

| | | | |
|----|----|--|--|
| | 36 | 4-[(N-hexyl,N-methyl-aminocarbonyl)-amino]phenyl, bistrifluoroacetate salt | 5.12 (d, 1H, J = 8.7 Hz), 3.40-3.10 (m, 6H), 2.99 (s, 3H), 2.95 (m, 2H), 1.56 (m, 2H), 1.31 (m, 6H), 0.88 (m, 3H) |
| 5 | 37 | 4-(3-hexyl-2-imidazolidinon-1-yl)phenyl, bistrifluoroacetate salt | 5.15 (m, 1H), 3.85 (m, 2H), 3.53 (m, 2H), 3.40-3.15 (m, 6H), 2.94 (m, 2H), 1.55 (m, 2H), 1.32 (m, 6H), 0.89 (m, 3H). |
| 10 | 38 | 4-[(1-oxoheptyl)-amino]phenyl, bistrifluoroacetate salt | 2.35 (tr, 2H, J=7.5 Hz), 1.65 (quint., 2H, J=7.1 Hz), 1.32 (m, 6H), 0.892 (tr, 3H, J=6.8Hz). |
| 15 | 39 | 4-[(1-oxo-4-phenylbutyl)amino]phenyl, bistrifluoroacetate salt | 7.34-7.25 (m, 4H), 7.15-7.05 (m, 5H), 2.71 (tr, 2H, J=7.7Hz), 2.36 (tr, 2H, J=7.4 Hz), 1.96 (m, 2H). |
| 20 | 40 | 4-[(propoxycarbonyl)-amino]phenyl | 4.07 (tr, 2H, J=6.6 Hz), 1.67 (sextet, 2H, J=7.0 Hz). 0.968 (tr, 3H, J=7.4 Hz). |
| 25 | 41 | 4-[[[(fur-2-ylmethyl)amino]carbonyl]amino]phenyl, bistrifluoroacetate salt | 7.40 (d, 1H, J = 0.9 Hz), 6.32 (dd, 1H, J = 2.9, 1.8 Hz), 6.23 (d, 1H, J = 2.9 Hz), 4.34 (s, 2H) |
| 30 | 42 | 4-[[[(2-phenylethyl)amino]carbonyl]amino]phenyl, bistrifluoroacetate salt | 7.38-7.02 (m, 9H), 3.50-3.15 (m, 6H), 2.80 (m, 2H) |
| | 43 | 4-[[[(2-indol-3-ylethyl)amino]carbonyl]amino]phenyl | 7.58-7.53 (m, 3 H), 7.42-7.30 (m, 4 H), 7.08-6.94 (m, 7H), 3.48 (tr, 2 H, J=6.9 Hz) 2.94 (tr, 2H, J=6.8 Hz). |
| | 44 | 4-[[[(octylamino)carbonyl]amino]phenyl, bistrifluoroacetate salt | 2.94 (m, 2H), 1.51 (tr, 2H, J=6.8 Hz), 1.30 (m, 10H), 0.884 (tr, 3H, J=6.9 Hz). |

- 68 -

| | | |
|----------|---|--|
| 45 5 | 1-[(hexylamino)carbonyl]indolin-5-yl | 7.83 (d, 2H, J = 9.2 Hz), 7.48 (m, 2H), 3.92 (t, 2H, J = 8.8 Hz), 3.1-3.2 (two overlap-ping t, 4H), 1.54 (m, 2H), 1.30 (m, 6H), 0.90 (t, 3H, J = 6.8 Hz). |
| 46 10 | 1-[(octylamino)carbonyl]indolin-5-yl | 7.83 (d, 2H, J = 9.2 Hz), 7.48 (m, 2H), 3.92 (t, 2H, J = 8.8 Hz), 3.1-3.2 (two overlap-ping t, 4H), 1.63 (m, 2H), 1.30 (m, 10H), 0.89 (t, 3H, J = 6.9 Hz). |
| 47 15 | 1-[(N-methyl-N-octylamino)carbonyl]indolin-5-yl | 7.53 (m, 2H), 6.90 (d, 1H, J = 8.3 Hz), 3.89 (t, 2H, J = 8.4 Hz), 3.26 (t, 2H, J = 7.6 Hz), 3.04 (t, 2H, J = 8.4 Hz), 2.91 (s, 3H), 1.60 (m, 2H), 1.27 (m, 10H), 0.87 (t, 3H, J = 6.8). |
| 48 20 | 1-(1-oxononyl)indolin-5-yl | 7.49 (m, 2H), 8.09 (d, 1H, J=9.1), 4.04 (t, 2H, J=8.5), 3.07 (t, 2H, J=8.5), 2.41 (t, 2H, J=7.5), 1.62 (m, 2H), 1.30 (m, 10H), 0.88 (t, 3H, J=6.8) |
| 49 25 | 1-(4-methylthiazol-2-yl)indolin-5-yl | 7.87 (d, 1H, J= 8.6 Hz), 7.58 (1H, dd, J = 2.0, 8.6 Hz), 7.52 (d, 1H, J = 2.0 Hz), 6.48 (s, 1H), 4.08 (t, 2H, J = 8.7 Hz), 3.25 (t, 2H, J = 8.7 Hz), 2.30 (s, 3H). |
| 50 30 | 1-(4-octylthiazol-2-yl)indolin-5-yl | 7.97 (d, 1H, J= 8.6 Hz), 7.57 (1H, dd, J = 2.0, 8.6 Hz), 7.53 (d, 1H, J = 2.0 Hz), 6.49 (s, 1H), 4.06 (t, 2H, J = 8.8 Hz), 3.24 (t, 2H, J = 8.8 Hz), 2.62 (t, 2H, J = 7.5 Hz), 1.68 (m, 2H), 1.2-1.4 (m, 10H), 0.88 (t, 3H, J = 7.0 Hz). |

- 69 -

| | | |
|----------|--|---|
| 51 5 | 1-(4-ethyl-5-methylthiazol-2-yl)indolin-5-yl | 7.87 (d, 1H, J = 8.5 Hz), 7.54 (1H, dd, J = 2.0, 8.5 Hz), 7.50 (d, 1H, J = 2.0 Hz), 4.02 (t, 2H, J = 8.7 Hz), 3.20 (t, 2H, J = 8.7 Hz), 2.56 (q, 2H, J = 7.7 Hz), 2.26 (s, 3H), 1.20 (t, 3H, J = 7.7 Hz). |
| 52 10 | 4-(3-octyl-2-imidazolidinon-1-yl)phenyl | 4.78 (m, 1H), 3.83 (m, 2H), 3.52 (m, 2H), 3.24 (t, 2H, 8Hz), 1.60-1.51 (m, 2H), 1.35-1.25 (m, 10H), 0.88 (t, 2H, 8Hz). |
| 53 15 | 4-[3-(4,4,4-trifluorobutyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt | 3.86 (m, 2H), 3.54 (m, 2H), 3.40-3.20 (m, 6H), 2.19 (m, 2H), 1.82 (quin, J = 7.9 Hz, 2H) |
| 54 20 | 4-[3-(3-phenylpropyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt | 7.20 (m, 4H), 7.10 (m, 1H), 5.15 (dd, 1H, 9.6,4Hz), 3.75 (m, 2H), 3.46 (m, 2H), 3.36-3.20 (m, 6H), 2.95-2.91 (m, 2H), 2.65 (t, 2H, 8Hz), 1.90 (qu, 2H, 8Hz). |
| 55 25 | 4-[3-(4,4,5,5,5-pentafluoropentyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt | 3.87 (m, 2H), 3.56 (m, 2H), 3.40-3.20 (m, 6H), 2.14 (m, 2H), 1.86 (quin, J = 7.8 Hz, 2H) |
| 56 30 | 4-[3-(2-cyclohexylethyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt | 3.82 (m, 2H), 3.50 (m, 2H), 2.87-2.70 (m, 6H), 1.78-1.63 (m, 5H), 1.41 (quartet, 2H, J=7.2 Hz), 1.30-1.18 (m, 4H), 0.949 (m, 2H). |
| 57 | 4-[3-[3-(4-chlorophenyl)propyl]-2-imidazolidinon-1-yl]phenyl | 7.19 (s, 4H), 4.79 (m, 1H), 3.74 (m, 2H), 3.47 (m, 2H), 3.30 (m, 2H), 2.63 (t, 2H, 7.6Hz), 1.91-1.83 (m, 2H). |

- 70 -

| | | | |
|----|----|---|---|
| | 58 | 4-(3-pentyl-2-imidazolidinon-1-yl)phenyl, bistrifluoroacetate salt | 3.82 (m, 2 H), 3.53 (m, 2H), 2.94 (m, 2H), 1.57 (quintet, 2H, J=7.4 Hz), 1.39-1.28 (m, 4H), 0.916, (tr, 3H, J=7.1 Hz). |
| 5 | 59 | 4-[3-(3-cyclopentylpropyl)-2-imidazolidinon-1-yl]phenyl | 3.81 (m, 2H), 3.51 (m, 2H), 3.23 (t, J = 7.3 Hz, 2H), 1.78 (m, 3H), 1.57 (m, 6H), 1.33 (m, 2H), 1.17 (m, 2H) |
| 10 | 60 | 4-[3-(2-cyclopentylethyl)-2-imidazolidinon-1-yl]phenyl, bistrifluoroacetate salt | 3.83 (m, 2H), 3.53 (m, 2H), 2.94 (m, 2H), 1.81 (m, 4H), 1.65-1.53 (m, 5H), 1.16 (m, 2H). |
| 15 | 61 | 4-[3-(3-cyclohexylpropyl)-2-imidazolidinon-1-yl]phenyl | 3.83 (m, 2H), 3.51 (m, 2H), 3.22 (t, J = 7.3 Hz, 2H), 1.71 (m, 5H), 1.56 (m, 2H), 1.20 (m, 6H), 0.88 (m, 2H) |
| 20 | 62 | 4-[3-(2,2-dimethylhexyl)-2-imidazolidinon-1-yl]phenyl | 3.82 (m, 2H), 3.60 (m, 2H), 3.03 (s, 2H), 1.28 (m, 6H), 0.93 (m, 3H), 0.91 (s, 6H) |
| 25 | 63 | 4-(3-hexyl-2-imidazolon-1-yl)phenyl | 6.93 (d, 1H, 4Hz), 6.70 (d, 1H, 4Hz), 4.79 (m, 1H), 3.64 (t, 2H, 8Hz), 1.71-1.64 (m, 2H), 1.35-1.28 (m, 6H), 0.91-0.86 (m, 3H). |
| | 64 | 4-[3-(4,4,4-trifluorobutyl)-2-imidazolon-1-yl]phenyl | 6.97 (d, 1H, 3Hz), 6.73 (d, 1H, 3Hz), 3.73 (t, 2H, 7Hz), 2.23-2.19 (m, 2H), 1.98-1.92 (m, 2H). |
| 30 | 65 | 4-(3-octyl-2-imidazolon-1-yl)phenyl | 6.93 (d, 1H, 4Hz), 6.69 (d, 1H, 4Hz), 3.64 (t, 2H, 7Hz), 1.70-1.63 (m, 2H), 1.33-1.23 (m, 10H), 0.90-0.85 (m, 3H). |

- 71 -

| | | | |
|----|----|---|--|
| | 66 | 4-[3-(3-cyclopentylpropyl)-2-imidazolon-1-yl]phenyl | 6.93 (d, 1H, 3Hz), 6.69 (d, 1H, 3Hz), 3.63 (t, 2H, 7Hz), 1.80-1.47 (m, 11H), 1.35-1.29 (m, 2H), 1.13-1.02 (m, 2H). |
| 5 | 67 | 4-(2-octyl-3-oxo-[1,2,4]-triazol-4-yl)phenyl | 8.25 (s, 1H), 3.79 (t, 2H, 7Hz), 1.80-1.70 (m, 2H), 1.36-1.25 (m, 10H), 0.91-0.86 (m, 3H). |
| 10 | 68 | 4-(4-hexyl-5-tetrazolon-1-yl)phenyl | 3.98 (t, 2H, J=7.1Hz), 2.9-2.7 (m, 6H), 1.82 (q, 2H, J=7 Hz), 1.4-1.27 (m, 6H), 0.89 (t, 3H, J=7Hz) |
| | 69 | 4-(4-octyl-5-tetrazolon-1-yl)phenyl | 3.98 (t, 2H, J=7.1Hz), 2.9-2.7 (m, 6H), 1.83 (m, 2H), 1.4-1.2 (m, 10H), 0.87 (t, 3H, J=7 Hz) |
| 15 | 70 | 4-[(3-cyclopentylpropyl)-5-tetrazolon-1-yl]phenyl | 3.97 (t, 2H, J=7.1Hz), 2.9-2.7 (m, 9H), 1.9-1.7 (m, 5H), 1.6 (m, 1H), 1.5 (m, 1H), 1.37(m, 2H), 1.07(m, 1H) |
| 20 | 71 | 4-(2-pentyloxazol-5-yl)phenyl | 7.48 (s, 1H), 4.82 (m, 1H), 2.92-2.70 (m, 8H), 1.80 (m, 2H), 1.39 (m, 4H), 0.92 (m, 4H) |
| | 72 | 4-(2-octyloxazol-5-yl)phenyl | 7.52 (s, 1H), 5.09 (m, 1H), 3.01-2.82 (m, 8H), 1.77 (m, 2H), 1.37-1.27 (m, 10H), 0.87 (m, 1H) |
| 25 | 73 | 4-[2-(2-cyclopentylethyl)oxazol-5-yl]phenyl | 7.52 (s, !H), 4.80 (m, 1H), 2.94-2.70 (m, 8H), 1.79 (m, 5H), 1.62 (m, 2H), 1.54 (m, 2H), 1.12 (m, 2H) |
| 30 | 74 | 4-[(4-ethyl-5-methylthiazol-2-yl)amino]phenyl | 7.62 (d, 2H, J = 9 Hz), 7.58 (d, 2H, J = 9 Hz), 2.53 (q, 2H, J = 7.5 Hz), 2.23 (s, 3H), 1.18 (t, 3H, J = 7.5 Hz) |

- 72 -

| | | | |
|----|----|--|--|
| | 75 | 4-[(4,5,6,7-tetrahydrobenzo-thiazol-2-yl)amino]phenyl | 7.54 (d, 2H, J = 9 Hz), 7.48 (d, 2H, J = 9 Hz), 2.54 (m, 2H), 2.50 (m, 2H), 1.75 (m, 4H) |
| 5 | 76 | 4-(2-hexylimidazol-4-yl)phenyl | 7.75 (s, 1H), 5.04 (m, 1H), 3.29-3.20 (m, 4H), 2.97-2.90 (m, 4H), 1.82 (m, 2H), 1.40-1.30 (m, 6H), 0.9 (m, 3H) |
| 10 | 77 | 4-(1-methyl-2-octylimidazol-5-yl)-phenyl | 7.92 (s, 1H), 5.30 (m, 1H), 4.84 (s, 3H), 3.48-3.25 (m, 4H), 3.05-2.95 (m, 4H), 1.80 (m, 2H), 1.50-1.26 (m, 10H), 0.89 (m, 3H) |
| 15 | 78 | 4-[1-methyl-2-(2-cyclopentylethyl)-imidazol-5-yl]phenyl | 7.41 (s, 1H), 3.64 (s, 3H), 2.96-2.68 (m, 8H), 1.90-1.79 (m, 9H), 1.16 (m, 2H) |
| 20 | 79 | 4-[1-methyl-2-[2-(4-fluorophenyl)ethyl]-imidazol-5-yl]phenyl | 7.40 (s, 1H), 7.10-6.95 (m, 4H), 4.91 (m, 1H), 3.39 (s, 3H), 3.0 (bs, 4H) |
| 25 | 80 | 4-(5-pentyl-[1,2,4]-oxadiazol-3-yl)phenyl | 2.96 (t, 2H, J=7.6Hz), 1.84 (t, 2H, J=7.4Hz), 1.39 (m, 4H), 0.92 (t, 3H, J=7.1) |
| 30 | 81 | 4-[5-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-3-yl]phenyl | 2.98 (t, 2H, J=7.5Hz), 1.84 (m, 5H), 1.70-1.50 (m, 4H), 1.16 (m, 2H) |
| | 82 | 4-(5-hexyl-[1,2,4]-oxadiazol-3-yl)phenyl | 2.96 (t, 2H, J=7.5Hz), 1.84 (quin, 2H, J=7.4Hz), 1.48-1.28 (m, 6H), 0.90 (t, 3H, J=7.0Hz) |
| | 83 | 4-(5-heptyl-[1,2,4]-oxadiazol-3-yl)phenyl | 2.96 (t, 2H, J=7.5Hz), 1.84 (quin, 2H, J=7.0Hz), 1.46-1.26 (m, 8H), 0.89 (t, 3H, J=6.9Hz) |

- 73 -

| | | |
|----------|---|---|
| 84 5 | 4-(5-hexylthio-[1,2,4]-triazol-3-yl)phenyl | 3.11(t,2H,J=7.3Hz), 2.98-2.84 (m,4H), 2.76 (t,2H,J=7.3Hz), 1.65 (q,2H,J=7.3Hz), 1.37 (q,2H,J=7.1Hz), 1.28-1.23 (m,4H), 0.84 (t,3H,J=6.9Hz) |
| 85 10 | 4-[[4-(4-propylpiperidin-1-yl)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]phenyl | 8.84 (s, 1H), 8.75(d, 1H, J=5.07 Hz), 8.46(d, 1H, J=8Hz), 7.15 & 7.08 each (d, 2H, J=8Hz), 0.92(t, 3H, J=7Hz) |
| 86 15 | 4-[[4-(hexylmethylamino)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]phenyl | 7.15(d, 2H, J=8.5Hz), 7.12(d, 2H, J=8.5Hz), 5.19(dd, 1H, 3.1Hz, 9Hz), 2.93(m, 2H), 0.90(t, 3H, 6.8Hz) |
| 87 20 | 4-[[4-(heptylmethylamino)-1,1-dioxo-[1,2,5]-thiadiazol-3-yl]amino]phenyl | 7.16(d, 2H, J=8.8Hz), 7.11(d, 2H, J=8.8 Hz), 5.01(dd, J=3.2Hz, 9.9Hz), 2.92(m, 2H), 1.68(m, 2H) |
| 88 25 | 4-(1-octyl-2,4-imidazolidinedion-3-yl)phenyl | 4.09 (s, 2H), 3.41 (t, 2H, 7hz), 1.65-1.56 (m, 2H), 1.30-1.25 (m, 10H), 0.91-0.86 (m, 3H). |
| 89 30 | 4-[3-(3-nitrophenyl)-5-pyrazolon-1-yl]phenyl | 8.55 (t,1H,J=1.9Hz), 8.47 (d, 1H,J=2.0Hz), 8.37 (dd,1H, J=3.2Hz), 8.14 (d,2H,J=8.9Hz), 8.08 (t,2H,J=8.5Hz), 7.74(d, 3H,J=8.9Hz), 7.56 (t,1H,J=8.0 Hz), 7.33 (dd,1H,J=4.8Hz), 7.04 (dd,4H,J=6.6Hz), 4.75 (t, 1H,J=2.1Hz), 2.83-2.69 (m,6H) |

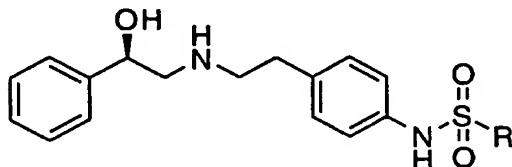
- 74 -

Starting with commercially available (R)-styrene epoxide and following the procedures outlined for Examples 17, 18 and 25, the compounds listed in Table 3 were prepared.

5

TABLE 3

10



15

20

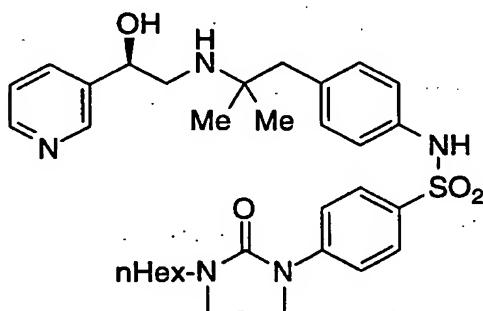
25

| Example | R | Selected ^1H NMR (CD_3OD) Data |
|---------|--|--|
| 90 | 4-iodophenyl, trifluoroacetate salt | 7.84 (d, 2H, $J = 8.6$ Hz), 7.45 (d, 2H, $J = 8.5$ Hz) |
| 91 | 2-naphthyl, trifluoroacetate salt | 8.31 (s, 1H), 7.96-7.90 (m, 3H), 7.74 (dd, 1H, $J = 1.8, 8.7$ Hz), 7.63 (t, 1H), 7.58 (t, 1H) |
| 92 | 3-quinolinyl, trifluoroacetate salt | 9.01 (d, 1H, $J = 2.2$ Hz), 8.75 (d, 1H, $J = 2.1$ Hz), 8.07 (d, 1H, $J = 8.4$ Hz), 8.03 (d, 1H, $J = 8.3$ Hz), 7.92 (t, 1H, $J = 7.0$ Hz), 7.72 (t, 1H, $J = 7.1$ Hz) |

25

EXAMPLE 93

30



- 75 -

(R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]-2-methylpropyl]phenyl]-4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonamide

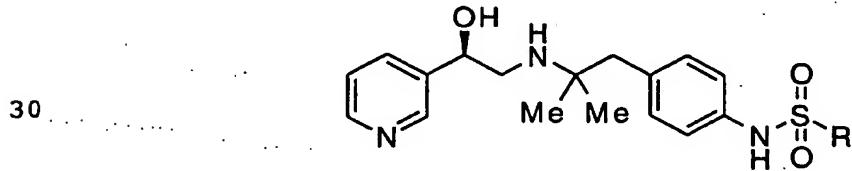
A solution of pyridine epoxide (160mg, 1.32 mmol) from example 16 and 4-amino-a,a-dimethylphenethylamine (1.2g, 7.3 mmol), prepared according to *J. Biol. Chem.* 1981, 256, 11944-50, in methanol (8 ml) was warmed at reflux for 16 hours. After cooling, the reaction mixture was concentrated and purified by flash chromatography (silica gel, 95:5 CH₂Cl₂: 10% NH₄OH/CH₃OH) to give 23 mg (0.080 mmol) of product as an oil.

The above product (18 mg, 0.063 mmol) was dissolved in CH₂Cl₂ (1 mL) and pyridine (0.05 mL). The resulting solution was cooled to 0°C and treated with 4-(3-hexyl-2-imidazolidinon-1-yl)benzenesulfonyl chloride (22 mg, 0.063 mmol). The mixture was allowed to stir at 0°C for 20 hours and was then purified by flash chromatography (silica gel, 95:5 CH₂Cl₂: 10% NH₄OH/CH₃OH) to give the desired product (21 mg, 0.035mmol) as an oil: ¹H NMR (CD₃OD) δ 8.53 (s, 1H), 8.44 (d, 1H, J=5.0), 7.83 (d, 1H, J=7.9), 7.63 (m, 4H), 7.40 (dd, 1H, J=5.0, 7.9), 6.98 (m, 4H), 4.72 (dd, 1H, J=4.0, 8.4), 3.80 (m, 2H), 3.49 (m, 2H), 3.22 (t, 2H, J=7.2), 2.78 (m, 2H), 2.62 (m, 2H), 1.55 (m, 2H), 1.31 (m, 6H), 1.01 (s, 3H), 0.99 (s, 3H), 0.89 (m, 3H).

Following the procedure outlined above, the compounds in Table 4 were prepared.

25

TABLE 4



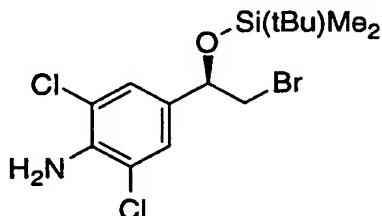
| Example | R | Selected ¹ H NMR (CD ₃ OD) Data |
|---------|---|---|
|---------|---|---|

- 76 -

| | | |
|---------|--------------------------------------|---|
| 5 94 | 4-iodophenyl | 7.82 (d, 2H, J=8.6), 7.42 (d, 2H, J=8.6) |
| 95 | 4-[[hexylamino]carbonyl]amino]phenyl | 7.55 (d, 2H, J=8.8), 7.42 (d, 2H, J=8.8), 3.11 (t, 2H, J=7.0), 1.49 (m, 2H), 1.30 (m, 6H), .089 (m, 3H) |

EXAMPLE 96

10



15

(R)-4-amino- α -(bromomethyl)-3,5-dichlorobenzene methanol, dimethyl-1,1-dimethylethylsilyl ether

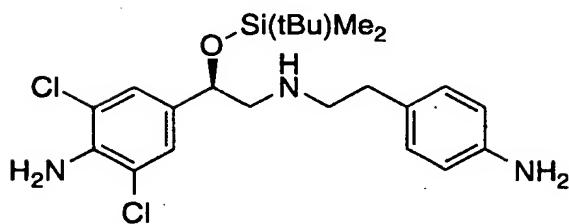
A solution of t-butyldimethylsilyl chloride (1.67 g, 11.1 mmol) in DMF (15 mL) was added slowly to a stirred solution of (R)-4-amino- α -(bromomethyl)-3,5-dichlorobenzene methanol (2.1 g, 7.4 mmol, see Judkins, et. al, European Patent Application 0 460 924) and imidazole (0.75 g, 11.1 mmol) in DMF (6 mL) with an ice-water bath cooling. After being stirred at RT for 3h, the reaction mixture was poured into water (300 mL) and the product was extracted with ether.

The organic phase was washed with saturated aqueous sodium bicarbonate solution, brine, dried($MgSO_4$) and evaporated to dryness. The crude product was purified on silica (95/5 hexane/ethyl acetate) to give the title compound (2.73 g, 93 %): 1H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 2H), 4.67 (dd, 1H, $J=2.1, 6.4$ Hz), 3.33 (m, 2H), 0.87 (s, 9H), 0.89 (s, 6H)

- 77 -

EXAMPLE 97

5

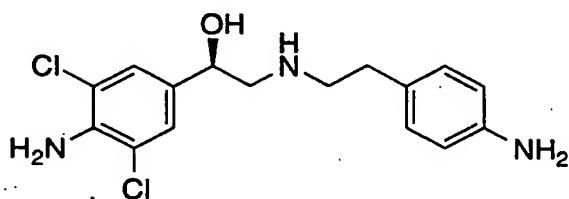


10 (R)-N-[2-[4-(Aminophenyl)]ethyl]-2-[(dimethyl-1,1-dimethylethylsilyl)oxy]-2-(4-amino-3,5-dichlorophenyl)ethylamine
 O-TBDMS bromo compound from Example 96 (2.73g, 6.86 mmol) was dissolved in CH₃CN (50 mL) and 4-amino-phenethylamine (1.86 g, 13.72 mmol) was added, followed by the addition of N,N'-diisopropylethylamine (3.58 mL, 20.6 mmol) and sodium iodide (1.03 g, 6.86 mmol). After being heated at reflux for 48 h, the reaction mixture was concentrated and the residue chromatographed on silica (50/50 ethyl acetate/hexane) to provide the title compound (2.3 g, 75 %): ¹H NMR (400 MHz, CDCl₃) δ 7.08 (s, 2H), 6.94 (AA', 2H, J=8.4 Hz), 6.60 (BB', 2H, J=8.4 Hz), 4.63 (m, 1H), 4.37 (s, 2H), 3.53 (br s, 2H), 2.87-2.60 (m, 6H), 0.80 (s, 9H), -0.03 (s, 6H)

25

EXAMPLE 98

30



(R)-N-[2-[4-(Aminophenyl)]ethyl]-2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethylamine

To a stirred solution of silyl compound from Example 97 (2.2 g, 4.8 mmol) in THF (20 mL) at RT was added

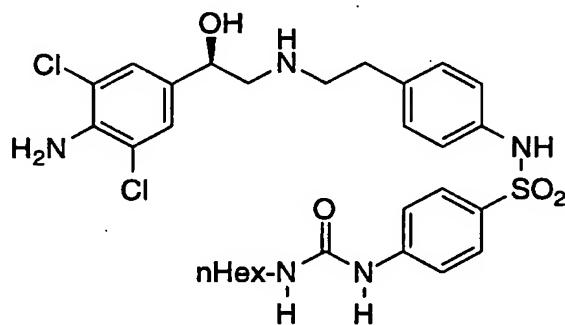
- 78 -

tetrabutylammonium fluoride (10 mL of 1.0 M solution in THF) in one portion. After being stirred at RT for 2h, the reaction mixture was concentrated and chromatographed on silica (10/90 CH₃OH/CH₂Cl₂) to give the title compound (1.59 g, 97 %): ¹H NMR (400 MHz, CD₃OD) δ 5 7.15 (s, 2H), 6.92 (AA', 2H, J=8.3 Hz), 6.60 (BB', 2H, 8.3 Hz), 4.58 (m, 1H), 2.83-2.65 (m, 6H)

EXAMPLE 99

10

15



20 (R)-N-[4-{[2-[2-Hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]ethyl}-4-(hexylaminocarbonylamino)benzenesulfonamide

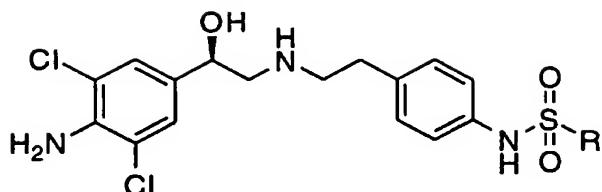
25 Following the procedure outlined in Example 18 and 25, the title compound was prepared from the aniline derivative from Example 98: NMR (400 MHz, CD₃OD) 7.57 (AA', 2H, J=2.7 Hz), 7.42 (BB', 2H, J=2.7 Hz), 7.16 (s, 2H), 7.04 (AA', 2H, J=2.0 Hz), 7.00 (BB', 2H, J=2.0 Hz), 4.58 (t, 1H, J=7.1 Hz), 3.14 (t, 1H, J=7.0 Hz), 2.80 (m, 2H), 2.73 (m, 4H), 1.49 (m, 2H), 1.32 (m, 6H), 0.90 (t, 3H, J=6.7 Hz). ESI MS m/z 622 (M).

30 Following the procedure outlined in Examples 96-99, the compounds in Table 5 were prepared.

- 79 -

TABLE 5

5

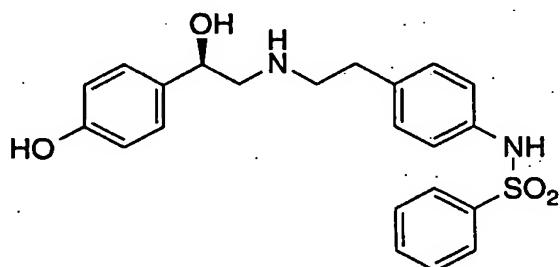


| Example | R | Selected ^1H NMR (CD_3OD) Data |
|-----------|---|---|
| 10 100 | 1-[(octylamino)carbonyl]-indolin-5-yl | 7.82 (d, 1H, $J=9.2$ Hz), 7.47 (m, 2H), 3.93 (t, 2H, $J=9.0$ Hz), 3.18 (m, 4H), 1.53 (m, 2H), 1.31 (m, 10H), 0.88 (t, 3H, $J=7.1$ Hz) |
| 15 101 | 4-(3-hexyl-2-imidazolidinon-1-yl)phenyl | 7.68-7.60 (AA'BB', 4H), 3.82 (t, 2H, $J=6.2$ Hz), 3.52 (t, 2H, $J=6.2$ Hz), 3.30 (t, 2H, $J=6.0$ Hz), 1.54 (m, 2H), 1.31 (m, 6H), 0.89 (t, 3H, $J=6.0$ Hz) |
| 20 102 | 4-(3-octyl-2-imidazolidinon-1-yl)phenyl | 7.65-7.60 (AA'BB', 4H), 3.82 (t, 2H, $J=6.2$ Hz), 3.52 (t, 2H, $J=6.2$ Hz), 3.29 (t, 2H, $J=6.0$ Hz), 1.54 (m, 2H), 1.30 (m, 10H), 0.87 (t, 3H, $J=6.1$ Hz) |

25

EXAMPLE 103

30



- 80 -

(R)-N-[4-[2-[[2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide

A solution of 5 g of 4-aminophenethyl alcohol in 50 mL of DMF was silylated with 5.5 g of t-butyldimethylsilyl chloride (TBDMS-Cl) and 2.5 g of imidazole overnight at room temperature. Extraction of the product following an aqueous ammonium chloride workup afforded 6.6 g of the O-TBDMS ether. This aniline derivative was then coupled to benzenesulfonyl chloride in pyridine-dichloromethane to give the sulfonamide in greater than 80% yield after chromatographic purification. The TBDMS group of the sulfonamide was removed with methanolic HCl at room temperature for 30 min. The crude alcohol was oxidized to the corresponding carboxylic acid with Jones reagent in acetone (RT 30 min, ethyl acetate extraction).

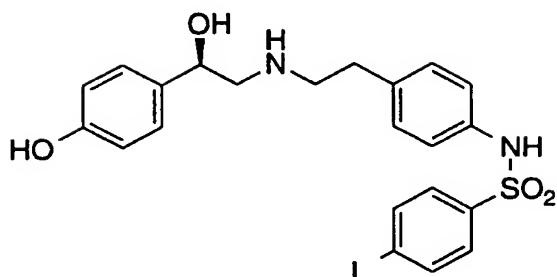
To a solution of 180 mg of (R)-octopamine and 300 mg of the resultant 4-N-benzenesulfonamidophenylacetic acid in 7 mL of DMF was added 0.5 mL of triethylamine and 490 mg of benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate. The reaction mixture was stirred at RT 2h, flash chromatography over silica gel eluting with 95:5 chloroform-methanol gave 322 mg of purified amide.

A solution of 220 mg of this amide in 13 mL of 1.0 M borane-THF was refluxed under argon for 2h followed by the addition of 3 mL of N,N-dimethylaminoethanol and further reflux for another hour. The solvent and excess volatiles were removed in vacuo and the residual solid was taken up in acetone and purified by PLC on silica gel (9:1 ethyl acetate:methanol) to yield 61 mg of the title compound: ¹H NMR (500 MHz, CD₃OD) δ 7.73 (dt, 2H, J=2.1, 8.2Hz), 7.53 (tt, 1H, J=1.4, 7.6Hz), 7.44 (t, 2H, J=8 Hz), 7.18 (d, 2H, J=8.4 Hz), 7.05 (ABq, 4H, J_{ab}=8.5 Hz), 6.76 (d, 2H, J=8.4Hz), 4.75 (dd, 1H, J=7.5, 7.6 Hz), 3.05-2.90 (m, 4H), 2.81 (t, 2H, J=7.6 Hz). Mass spec calcd. 412.5 found 413.2.

- 81 -

EXAMPLE 104

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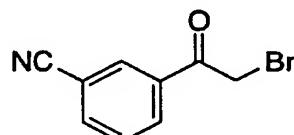
(R)-N-[4-{2-[(2-Hydroxy-2-(4-hydroxyphenyl)ethyl)amino]ethyl}phenyl]-4-iodobenzenesulfonamide

15 Following the procedure outlined in Example 103, the title compound was prepared: ^1H NMR (500 MHz, CD_3OD) δ 7.77 (d, 2H, $J=8.5$ Hz), 7.43 (d, 2H, $J=8.5$ Hz), 7.15 (d, 2H, $J=8.5$ Hz), 7.02 (ABq, 4H, $J_{\text{ab}}=8.7$ Hz), 6.75 (d, 2H, $J=8.5$ Hz), 4.67 (dd, 1H, $J=4.4, 6.6$ Hz), 2.90-2.66 (m, 6H). Mass spec calcd. 538.4 found 538.9.

20

EXAMPLE 105

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3-(2-bromoacetyl)benzonitrile

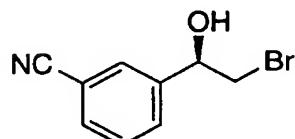
To a solution of 1.02 g (7.04 mmol) of 3-acetylbenzonitrile in 70 mL of ethyl ether was added 1.02 g (3.52 mmol, 0.5 equiv) of 30 dibromobarbituric acid. The mixture was allowed to stir at room temperature overnight. The resultant white slurry was filtered and the filtrate was concentrated. Purification by flash chromatography (silica gel, 20% ethyl acetate/hexane) gave 1.28 g (81%) of the title compound as a white solid: ^1H NMR (400 MHz, CDCl_3) δ .8.26 (t, 1H, $J = 1.4$

- 82 -

Hz), 8.20 (td, 1H, J = 1.5, 8.0 Hz), 7.87 (dd, 1H, J = 1.3, 7.8 Hz), 7.64 (t, 1H, J = 7.9 Hz), 4.40 (s, 2H).

EXAMPLE 106

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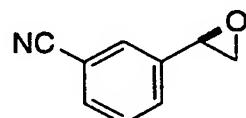
10

(R)- α -Bromomethyl-3-cyanophenylmethanol

- To a suspension of 181 mg (0.623 mmol) of (R)-tetrahydro-1-methyl-3,3-diphenyl-1*H,3H*-pyrrolo[1,2*c*][1,3,2]oxazaborole-borane (*R*-OAB catalyst) in 6 mL of THF at 0 °C was added dropwise 6.24 mL (6.24 mmol) of a 1 M solution of borane in THF. The resultant clear solution was allowed to stir for 5 min, and then a solution of 1.27 g (5.67 mmol) of bromoketone from Example 105 in 6 mL of THF was added slowly over 1 h. After the reaction was allowed to stir for 30 min more, it was quenched by the dropwise addition of 6 mL of methanol and concentrated. Purification by flash chromatography (silica gel, 20-25% ethyl acetate/hexane) provided 944 mg (74%) of the title compound as a clear oil which crystallized: ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, 1H, J = 1.5 Hz), 7.62-7.60 (m, 2H), 7.48 (t, 1H, J = 7.7 Hz), 4.95 (dd, 1H, J = 3.4, 8.4 Hz), 3.63 (dd, 1H, J = 3.4 Hz), 3.49 (dd, 1H, J = 8.4 Hz).

EXAMPLE 107

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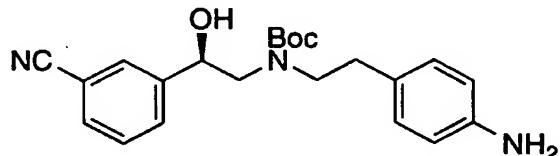
(R)-(3-cyanophenyl)oxirane

- 83 -

To a solution of 937 mg (4.14 mmol) of bromohydrin from Example 106 in 8 mL of methanol was added 601 mg (4.35 mmol, 1.05 equiv) of potassium carbonate. The reaction mixture was allowed to stir at room temperature for 7 h. It was then diluted with ethyl acetate, washed with water, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (silica gel, 20% ethyl acetate/hexane) provided 573 mg (95%) of the title compound: ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.55 (m, 2H), 7.49 (dd, 1H, J = 1.6, 7.9 Hz), 7.44 (t, 1H, J = 7.7 Hz), 3.87 (dd, 1H, J = 2.5, 4.0 Hz), 3.17 (dd, 1H, J = 4.1, 5.5 Hz), 2.74 (dd, 1H, J = 2.5, 5.4 Hz).

EXAMPLE 108

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(*R*)-N-[2-[4-(aminophenyl)]ethyl]-2-hydroxy-2-(3-cyanophenyl)ethylcarbamic acid 1,1-dimethylethyl ester

25

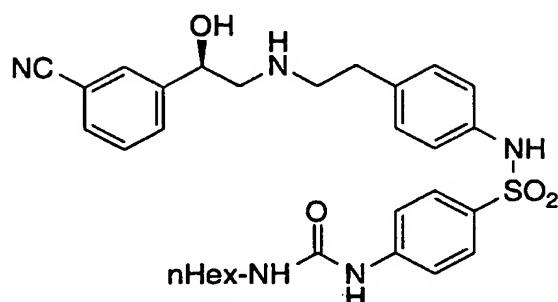
Following the procedures outlined in Examples 17 and 18, the title compound was prepared from the epoxide from Example 107: ¹H NMR (400 MHz, CDCl₃) δ 7.58-7.52 (br m, 3H), 7.41 (t, 1H, J = 7.5 Hz), 6.89 (br d, 2H, J = 7.6 Hz), 6.65 (br d, 2H, J = 7.8 Hz), 4.82 (br dd, 1H, J = 2.7, 7.9 Hz), 3.42-3.05 (br m, 4H), 2.75-2.55 (br m, 2H).

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- 84 -

EXAMPLE 109

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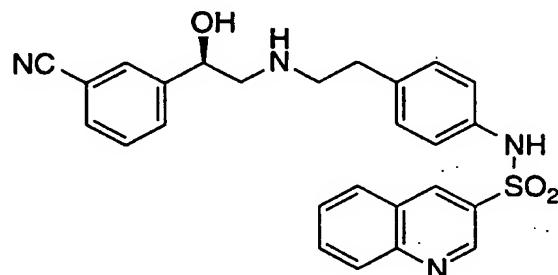
(R)-N-[4-{2-[(2-Hydroxy-2-(3-cyanophenyl)ethyl)amino]ethyl}phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide

15 Following the procedure outlined in Example 25, the title compound was prepared from the Boc aniline derivative from Example 108: ^1H NMR (400 MHz, CD₃OD) δ 7.70 (s, 1H), 7.63-7.57 (m, 4H), 7.48 (t, 1H, J = 7.7 Hz), 7.43 (d, 2H, J = 8.9 Hz), 7.06 (d, 2H, J = 8.5 Hz), 6.99 (d, 2H, J = 8.5 Hz), 4.77 (dd, 1H, J = 3.9, 8.5 Hz), 3.15 (t, 2H, J = 7.0 Hz), 2.86-2.69 (m, 6H), 1.49 (br m, 2H), 1.31 (br m, 6H), 0.90 (br t, 3H).

20

EXAMPLE 110

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(R)-N-[4-{2-[(2-hydroxy-2-(3-cyanophenyl)ethyl)amino]ethyl}phenyl]-3-quinolinesulfonamide

Following the procedure outlined in Example 25, the title compound was prepared from the Boc aniline derivative from Example

- 85 -

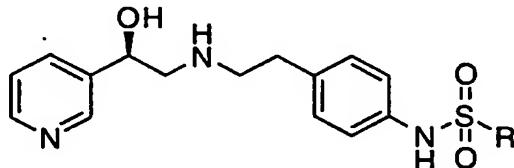
108 and 3-quinolinesulfonyl chloride: ^1H NMR (400 MHz, CD₃OD) δ 9.02 (d, 1H, J = 2.3 Hz), 8.68 (d, 1H, J = 1.9 Hz), 8.06 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 7.9 Hz), 7.90 (ddd, 1H, J = 1.4, 7.0, 8.4 Hz), 7.72-7.69 (m, 2H), 7.62-7.58 (m, 2H), 7.47 (t, 1H, J = 7.7 Hz), 7.07 (d, 2H, J = 8.7 Hz), 7.03 (d, 2H, J = 8.7 Hz), 4.76 (dd, 1H, J = 4.0, 8.5 Hz), 2.85-2.68 (m, 6H).

Following the procedures outlined for Examples 14-31, the compounds listed in Table 6 were prepared.

10

TABLE 6

15



20

| Example | R | Selected ^1H NMR (CD ₃ OD) Data |
|---------|---|---|
| 111 | 4-(3-hexyl-2,4-imidazolidinedion-1-yl)phenyl | 4.40 (s, 2H), 3.54 (m, 2H), 1.68-1.59 (m, 2H), 1.37-1.28 (m, 6H), 0.91 (m, 3H). |
| 112 | 4-(3-octyl-2,4-imidazolidinedion-1-yl)phenyl | 4.40 (s, 2H), 3.52 (m, 2H), 1.68-1.59 (m, 2H), 1.38-1.23 (m, 10H), 0.89 (m, 3H). |
| 113 | 4-[2-(4-cyclohexylbutyl)-oxazol-5-yl]phenyl, trihydrochloride | 7.66 (s, 1H), 5.35 (m, 1H), 3.22-3.32 (m, 5H), 2.95 (m, 2H), 2.90 (t, J=6.5Hz, 2H), 1.8 (m, 2H), 1.69 (m, 5H), 1.45 (m, 2H), 1.24 (m, 6H), 0.89 (m, 2H) |
| 114 | 4-[2-[2-(4-fluorophenyl)ethyl]-oxazol-5-yl]phenyl | 7.49 (s, 1H), 7.2 (m, 2H), 6.99 (m, 2H), 4.90 (m, 1H), 3.05 (m, 4H), 2.70-2.85 (m, 6H) |

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- 86 -

| | | | |
|----|-----|--|---|
| | 115 | 4-[2-(3-cyclopentylpropyl)-oxazol-5-yl]phenyl | 7.51 (s, 1H), 4.90 (m, 1H), 2.65-2.90 (m, 8H), 1.80 (m, 5H), 1.46-1.62 (m, 4H), 1.05 (m, 2H) |
| 5 | 116 | 4-(4-hexyl-3-oxo-[1,2,4]-triazol-2-yl)phenyl | 8.04 (s, 1H), 3.69 (m , 2H), 1.78-1.69 (m, 2H), 1.39-1.28 (m, 6H), 0.90 (m, 3H). |
| 10 | 117 | 4-(4-octyl-3-oxo-[1,2,4]-triazol-2-yl)phenyl | 8.03 (s, 1H), 3.69 (m , 2H), 1.77-1.69 (m, 2H), 1.38-1.25 (m, 10H), 0.89 (m, 3H). |
| | 118 | 4-(4-heptyl-5-methyl-[1,2,3]-triazol-2-yl)phenyl | 2.28 (s,3H), 1.67 (t, 2H, J=6.9 Hz), 1.36-1.34 (m, 4H), 1.31-1.29 (m, 2H), 1.18 (d, 4H, J=2.5 Hz), 0.88 (t, 3H, J=7.0 Hz) |

15

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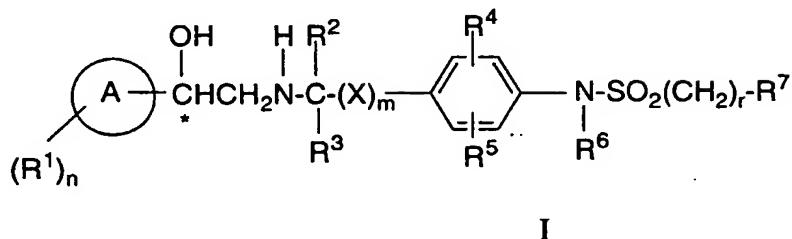
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- 87 -

WHAT IS CLAIMED IS:

1. A compound having the formula I:

5



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where

n is 0 to 5;

m is 0 or 1;

r is 0 to 3;

A is (1) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
 (2) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
 (3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,
 (4) phenyl, or
 (5) a benzene ring fused to a C₃-C₈ cycloalkyl ring;

25 R¹ is

- (1) hydroxy,
- (2) oxo,
- (3) halogen,
- (4) cyano,
- (5) NR₈R₈,
- (6) SR₈,
- (7) trifluoromethyl,

30

- 88 -

- (8) C₁-C₁₀ alkyl,
(9) OR⁸,
(10) SO₂R⁹,
5 (11) OCOR⁹,
(12) NR⁸COR⁹,
(13) COR⁹,
(14) NR⁸SO₂R⁹,
(15) NR⁸CO₂R⁸, or
(16) C₁-C₁₀ alkyl substituted by hydroxy, halogen, cyano,
10 NR⁸R⁸, SR⁸, trifluoromethyl, OR⁸, C₃-C₈ cycloalkyl,
phenyl, NR⁸COR⁹, COR⁹, SO₂R⁹, OCOR⁹, NR⁸SO₂R⁹ or
NR⁸CO₂R⁸;

R² and R³ are independently

- 15 (1) hydrogen,
(2) C₁-C₁₀ alkyl or
(3) C₁-C₁₀ alkyl with 1 to 4 substituents selected from
hydroxy, C₁-C₁₀ alkoxy, and halogen;

X is (1) -CH₂-,

- 20 (2) -CH₂-CH₂-,
(3) -CH=CH- or
(4) -CH₂O-;

R⁴ and R⁵ are independently

- 25 (1) hydrogen,
(2) C₁-C₁₀ alkyl,
(3) halogen,
(4) NHR⁸,
(5) OR⁸,
(6) SO₂R⁹ or
(7) NHSO₂R⁹;

30 R⁶ is (1) hydrogen or
(2) C₁-C₁₀ alkyl;

R⁷ is Z-(R^{1a})_n;

R^{1a} is (1) R¹, with the proviso that when A is phenyl, R^{1a} is not
C₁-C₁₀ alkyl,

- 89 -

- (2) C₃-C₈ cycloalkyl,
(3) phenyl optionally substituted with up to 4 groups
independently selected from R⁸, NR⁸R⁸, OR⁸, SR⁸ and
halogen, or
5 (4) 5 or 6-membered heterocycle with from 1 to 4
heteroatoms selected from oxygen, sulfur and nitrogen,
optionally substituted with up to four groups independently
selected from oxo, R⁸, NR⁸R⁸, OR⁸, SR⁸, and halogen;
- Z is
10 (1) phenyl,
(2) naphthyl,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4
heteroatoms selected from oxygen, sulfur and nitrogen,
(4) a benzene ring fused to a C₃-C₈ cycloalkyl ring,
15 (5) a benzene ring fused to a 5 or 6-membered heterocyclic
ring with from 1 to 4 heteroatoms selected from oxygen,
sulfur and nitrogen,
(6) a 5 or 6-membered heterocyclic ring with from 1 to 4
heteroatoms selected from oxygen, sulfur and nitrogen
fused to a 5 or 6-membered heterocyclic ring with from 1
20 to 4 heteroatoms selected from oxygen, sulfur and
nitrogen, or
(7) a 5 or 6-membered heterocyclic ring with from 1 to 4
heteroatoms selected from oxygen, sulfur and nitrogen
fused to a C₃-C₈ cycloalkyl ring;
- R⁸ is
25 (1) hydrogen,
(2) C₁-C₁₀ alkyl,
(3) C₃-C₈ cycloalkyl,
(4) Z optionally having 1 to 4 substituents selected from
halogen, nitro, oxo, NR¹⁰R¹⁰, C₁-C₁₀ alkyl, C₁-C₁₀
30 alkoxy, C₁-C₁₀ alkylthio, and C₁-C₁₀ alkyl having 1 to 4
substituents selected from hydroxy, halogen, CO₂H, CO₂-
C₁-C₁₀ alkyl, SO₂-C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₁-
C₁₀ alkoxy, and Z optionally substituted by from 1 to 3 of
halogen, C₁-C₁₀ alkyl or C₁-C₁₀ alkoxy, or

- 90 -

(5) C₁-C₁₀ alkyl having 1 to 4 substituents selected from hydroxy, halogen, CO₂H, CO₂-C₁-C₁₀ alkyl, SO₂-C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkyl, and Z optionally substituted by from 1 to 4 of halogen, C₁-C₁₀ alkyl or C₁-C₁₀ alkoxy;

5 R⁹ is (1) R⁸ or

(2) NR⁸R⁸;

R¹⁰ is (1) C₁-C₁₀ alkyl, or

10 (2) two R¹⁰ groups together with the N to which they are attached formed a 5 or 6-membered ring optionally substituted with C₁-C₁₀ alkyl; or a pharmaceutically acceptable salt thereof.

15 2. A compound of Claim 1 where n is 0 to 3;

m is 1;

r is 0 to 2;

A is phenyl or a 5- or 6-membered heterocyclic ring with from 1 to 4 nitrogen atoms;

20 X is -CH₂-;

R¹ is (1) hydroxy,

(2) halogen,

(3) cyano,

(4) trifluoromethyl,

25 (5) NR⁸R⁸,

(6) NR⁸SO₂R⁹,

(7) NR⁸COR⁹,

(8) NR⁸CO₂R⁸, or

(9) C₁-C₁₀ alkyl optionally substituted by hydroxy;

30 R², R³ are independently

(1) hydrogen or

(2) methyl;

R⁴, R⁵ and R⁶ are each hydrogen;

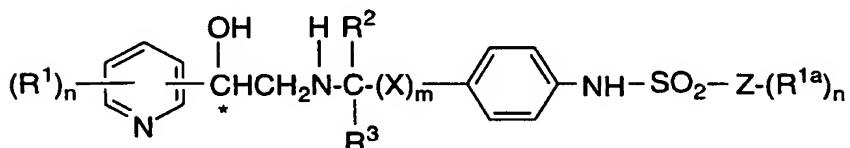
R⁷ is Z-(R^{1a})_n; and

- 91 -

R⁸, R⁹, Z and R^{1a} are as defined in Claim 1, and when R¹ is part of the definition of R^{1a} has the meaning defined in Claim 1.

3. A compound of Claim 1 having the formula Ia:

5



10

Ia

wherein

- n is 0 to 3;
- 15 m is 1
- R¹ is (1) halogen or
(2) NR⁸R⁸;
- R², R³ are independently hydrogen or methyl;
- R^{1a} is (1) halogen,
20 (2) C₁-C₁₀ alkyl,
(3) NR⁸R⁸,
(4) NR⁸COR⁹,
(5) NR⁸CO₂R⁸,
(6) COR⁹,
25 (7) OCOR⁹, or
(8) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to four groups independently selected from oxo, halogen, R⁸, NR⁸R⁸, OR⁸, and SR⁸;
- 30 Z is (1) phenyl,
(2) naphthyl,
(3) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen,

- 92 -

(4) benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen, or

5

(5) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a C₃-C₈ cycloalkyl ring;

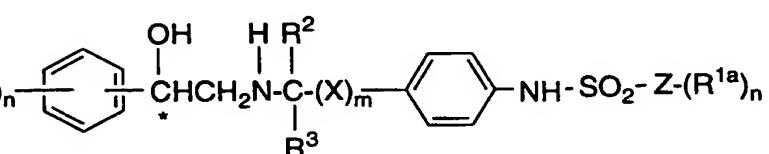
X is -CH₂-; and

R⁸ and R⁹ are as defined in Claim 1.

10

4. A compound of Claim 3 wherein R² and R³ are each hydrogen.

15



20

Ib

wherein

25

n is 0 to 3;

m is 1

R¹ is (1) hydroxy,

(2) cyano,

(3) NR⁸R⁸ or

(4) halogen;

30

R^{1a} is (1) halogen,

(2) NR⁸R⁸,

(3) NR⁸COR⁹,

(4) NR⁸CO₂R⁸,

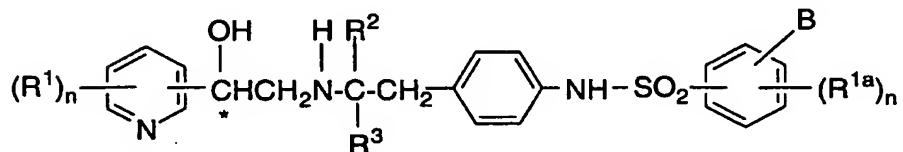
(5) OCOR⁹, or

- 93 -

(6) a 5 or 6-membered heterocycle with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, optionally substituted with up to three groups independently selected from oxo, halogen, R⁸, NR⁸R⁸, OR⁸ and SR⁸;

5 Z is (1) phenyl,
(2) naphthyl or
(3) benzene ring fused to a 5 or 6-membered heterocyclic
ring with from 1 to 4 heteroatoms selected from oxygen,
sulfur and nitrogen;
10 X is -CH₂-; and
R² and R³ are independently hydrogen or methyl.

6. A compound of Claim 1 having the formula Id



Id

n is 0 or 1;
 R^1 is NR^8R^8 ;
 R^2 and R^3 are independently

25 (1) hydrogen, or
 (2) methyl:

B is (1) hydrogen

30 B is (1) hydrogen,
 (2) benzene fused to the benzene ring to form naphthyl, or
 (3) a 5 or 6-membered heterocycle with 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen atom fused to the benzene ring;

R^{1a} is (1) halogen,
 (2) C₁-C₁₀ alkyl,
 (3) NR⁸R⁸,
 (4) NR⁸COR⁹,

- 94 -

- (5) $\text{NR}^8\text{CO}_2\text{R}^8$,
(6) COR^9 , or
(7) a 5 or 6-membered heterocycle with from 1 to 4
5 heteroatoms selected from oxygen, sulfur and nitrogen,
optionally substituted with up to four groups independently
selected from oxo, R^8 , SR^8 , OR^8 , and NR^8R^8 ;
when B and the benzene ring form a fused ring system, R^{1a}
is attached to either ring;
- 10 R^8 is (1) hydrogen,
(2) $\text{C}_1\text{-C}_{10}$ alkyl,
(3) Z optionally having 1 to 4 substituents selected from
nitro, oxo, and $\text{NR}^{10}\text{R}^{10}$, or
(5) $\text{C}_1\text{-C}_{10}$ alkyl having 1 to 4 substituents selected from
hydroxy, halogen, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, and Z
15 optionally substituted by from 1 to 4 of halogen, $\text{C}_1\text{-C}_{10}$
alkyl or $\text{C}_1\text{-C}_{10}$ alkoxy;
- 15 R^9 is (1) R^8 or
(2) NR^8R^8 ;
- 20 R^{10} is (1) $\text{C}_1\text{-C}_{10}$ alkyl, or
(2) two R^{10} groups together with the N to which they are
attached formed a 5 or 6-membered ring optionally
substituted with $\text{C}_1\text{-C}_{10}$ alkyl; and
- 25 Z is (1) phenyl,
(2) a 5 or 6-membered heterocyclic ring with from 1 to 4
heteroatoms selected from oxygen, sulfur and nitrogen,
(3) a benzene ring fused to a 5 or 6-membered heterocyclic
ring with from 1 to 4 heteroatoms selected from oxygen,
sulfur and nitrogen, or
(4) a 5 or 6-membered heterocyclic ring with from 1 to 4
30 heteroatoms selected from oxygen, sulfur and nitrogen
fused to a $\text{C}_3\text{-C}_8$ cycloalkyl ring.

7. A compound of Claim 1 selected from the group
consisting of:

- 95 -

- N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-4-iodobenzenesulfonamide;
N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-2-naphthalenesulfonamide; and
- 5 N-[4-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-quinolinesulfonamide.
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]-ethyl]-phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide
10 N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]-ethyl]-phenyl]-1-[(octylamino)carbonylamino]-5-indolinesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]-ethyl]-phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-amino-3,5-dichlorophenyl)ethyl]amino]-ethyl]-phenyl]-4-(3-octyl-2-imidazolidon-1-yl)benzenesulfonamide
- 15 N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-ethyl]phenyl]-benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(4-hydroxyphenyl)ethyl]amino]-ethyl]phenyl]-4-iodobenzenesulfonamide
20 N-[4-[2-[[2-hydroxy-2-(3-cyanophenyl)ethyl]amino]-ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide, and
N-[4-[2-[[2-hydroxy-2-(3-cyanophenyl)ethyl]amino]-ethyl]phenyl]-3-quinolinesulfonamide

8. A compound of Claim 1 selected from the group
25 consisting of:
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide;
30 N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide;

- 96 -

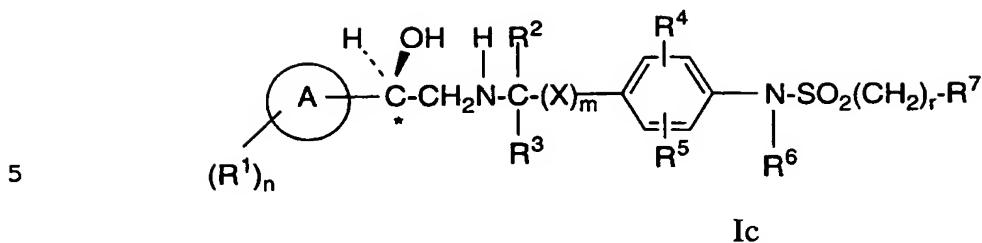
- N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-5-benzisoxazolesulfonamide;
5 N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[(dimethylaminocarbonyl)amino]benzenesulfonamide;
10 N-[4-[2-[[2-hydroxy-2-(6-aminopyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(hexylaminocarbonylamino)benzenesulfonamide;
15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-isopropylbenzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-2-naphthalenesulfonamide;
20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-3-quinolinesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(hexylmethylaminocarbonyl)amino]benzenesulfonamide;
25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolidon-1-yl)benzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-iodobenzenesulfonamide;
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2-imidazolidon-1-yl]benzenesulfonamide
30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolidinon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-hexyl-2-imidazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(3-octyl-2-imidazolon-1-yl)benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[3-(3-cyclopentylpropyl)-2-imidazolon-1-yl]benzenesulfonamide
N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-1-(4-octylthiazol-2-yl)-5-indolinesulfonamide

- 97 -

- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-pentyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-hexyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
- 5 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-heptyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(5-octyl-[1,2,4]-oxadiazol-3-yl)benzenesulfonamide
- 10 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(2-cyclopentylethyl)-[1,2,4]-oxadiazol-3-yl]benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[5-(3-cyclopentylpropyl)-[1,2,4]-oxadiazol-3-yl]benzenesulfonamide
- 15 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-pentyloxazol-5-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-hexyloxazol-5-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-heptyloxazol-5-yl)benzenesulfonamide
- 20 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(2-octyloxazol-5-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(2-cyclopentylethyl)oxazol-5-yl]benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[2-(3-cyclopentylpropyl)oxazol-5-yl]benzenesulfonamide
- 25 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-hexyl-5-tetrazolon-1-yl)benzenesulfonamide
- N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-(4-octyl-5-tetrazolon-1-yl)benzenesulfonamide
- 30 N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[(3-cyclopentylpropyl)-5-tetrazolon-1-yl]benzenesulfonamide

9. A compound of Claim 1 with the structural formula
Ic:

- 98 -



where n, m, r, A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and X are as defined in
Claim 1.

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10 A method for the treatment of diabetes which comprises administering to a diabetic patient an effective amount of a compound of Claim 1.

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11. A method for the treatment of obesity which comprises administering to an obese patient an effective amount of a compound of Claim 1.

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12. A method for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels which comprises administering to a patient needing lower triglyceride and cholesterol levels or higher high density lipoprotein levels an effective amount of a compound of Claim 1.

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13. A method for decreasing gut motility which comprises administering to a patient in need of decreased gut motility, an effective amount of a compound of Claim 1.

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14. A method for reducing neurogenic inflammation of airways which comprises administering to a patient in need of reduced neurogenic inflammation, an effective amount of a compound of Claim 1.

- 99 -

15. A method for reducing depression which comprises administering to a depressed patient an effective amount of a compound of Claim 1.

5 16. A method for treating gastrointestinal disorders which comprises administering to a patient with gastrointestinal disorders an effective amount of a compound of Claim 1.

10 17. A composition for the treatment of diabetes or obesity or for lowering triglyceride or cholesterol levels or increasing high density lipoprotein levels or for decreasing gut motility or for reducing neurogenic inflammation or for treating depression or for treating gastrointestinal disorders which comprises an inert carrier and an effective amount of a compound of Claim 1.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/04956

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| A. CLASSIFICATION OF SUBJECT MATTER |
| IPC 6 C07D213/30 C07D413/12 C07D401/12 C07D417/14 C07C311/21 |
| C07D417/12 C07D209/08 C07D233/36 C07D215/36 A61K31/44 |
| A61K31/47 A61K31/18 |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X, P | EP-A-0 611 003 (MERCK & CO INC) 17 August 1994 see the whole document --- | 1-17 |
| A | EP-A-0 091 749 (BEECHAM GROUP PLC) 19 October 1983 see the whole document ----- | 1-17 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

4 August 1995

Date of mailing of the international search report

11.08.95

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Authorized officer

Bosma, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No'

PCT/US 95/04956

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|----------|------------------|
| EP-A-0611003 | 17-08-94 | AU-B- | 5498694 | 29-06-95 |
| | | CA-A- | 2114712 | 10-08-94 |
| | | JP-A- | 7010827 | 13-01-95 |
| | | WO-A- | 9418161 | 18-08-94 |
| EP-A-0091749 | 19-10-83 | JP-A- | 58185554 | 29-10-83 |